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Psychometric performance and clinical meaningfulness of the Patient Assessment of Constipation – Quality of Life questionnaire in prucalopride (RESOLOR®) trials for chronic constipation

D. DUBOIS,* H. GILET,† M. VIALA-DANTEN† & J. TACK‡

*Patient Value Solutions, Huldenberg, Belgium
†Mapi Values, Lyon, France
‡Division of Gastroenterology, University Hospital, Leuven, Belgium

Abstract

Background *The Patient Assessment of Constipation–Quality of Life (PAC-QOL) is a self-reported questionnaire measuring health-related quality of life (HRQL) of constipated patients and was used as secondary endpoint in three identical double-blind, randomized, placebo-controlled Phase III clinical trials. These 12-week trials in subjects with severe chronic constipation evaluated the effects of prucalopride, a selective 5-HT$_4$ agonist given orally once daily.* ***Methods*** *To consolidate the main treatment effect results observed in the prucalopride trial populations, analyses were undertaken on the pooled data of the three trials to confirm the psychometric properties of the PAC-QOL and to provide guidance for the interpretation of the clinical significance of its scores.* ***Key Results*** *The evaluation of the psychometric properties confirmed the PAC-QOL reliability, validity and responsiveness to measure the impact of chronic constipation symptoms on HRQL in the prucalopride trials. The 1-point improvement in PAC-QOL scores used as target response level for the main treatment effect analyses was validated as a relevant definition of response for treatment group comparisons. Cumulative distribution curves, drawn for each treatment group to provide more complete information on treatment effects than single minimal important difference point estimates, demonstrated consistent superior effects of prucalopride over placebo on all PAC-QOL scores.* ***Conclusions & Inferences*** *The PAC-QOL questionnaire is a useful measurement tool to assess, from a patient perspective, the potential therapeutic value of chronic constipation treatments in clinical trials and, by directly reflecting the patient's own perspective on constipation and its treatment, eventually also for informing daily medical practice.*

Keywords *chronic constipation, clinical meaningfulness, health-related quality of life, PAC-QOL, prucalopride, psychometric properties.*

INTRODUCTION

Chronic constipation is a common gastrointestinal disorder mainly affecting children,[1] women and the elderly. Depending on definitions and methods used, estimates indicate that 10–15% of the general adult population suffer from constipation.[2–4] Commonly used definitions of constipation rely on what is considered a normal stool frequency. However, patients with chronic constipation typically report that stool voiding is not only infrequent, but stool is also too hard or too difficult to pass, or incomplete and therefore unsatisfactory. Other frequently reported symptoms include bloating and abdominal pain or discomfort.[5] Several studies conducted in adults have shown a negative impact of chronic constipation on health-related quality of life,[6–8] with levels of impairment comparable to those observed in patients suffering from gastro-oesophageal reflux or in women with a

Address for correspondence
Dominique Dubois MD,
PVS Consultancy bvba, Kleinwaverstraat 48, B-3040,
Huldenberg, Belgium.
Tel: +32 16 47 20 67; fax: +32 14 40 43 91;
e-mail: dominique@pvsconsultancy.com
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history of hypertension, diabetes, heart disease or depression.[9]

The self-reported Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire was developed based on the literature, clinical expert interviews and patient interviews to measure health-related quality of life of constipated patients. It achieved good psychometric properties during the observational 6-week validation study conducted in the USA with constipated adults.[10] The PAC-QOL was shown to be a brief but comprehensive measure of the burden of constipation on patients' everyday life and is available in several languages, allowing its use in international clinical trials. The PAC-QOL was then used as a secondary endpoint in three large Phase III trials evaluating the efficacy, safety and impact on health-related quality of life of oral prucalopride (2 mg and 4 mg) given once daily for 12 weeks in patients with chronic constipation. Prucalopride is a highly selective 5-HT_4 agonist, effective for treatment of chronic constipation, as demonstrated in three pivotal Phase III trials and a trial in elderly patients.[11–14]

During the three prucalopride trials using the PAC-QOL, the proportion of patients with an improvement of at least 1 point on the PAC-QOL subscales, ranging from 0 to 4, during active or placebo treatment was reported. However, the 1-point improvement threshold was defined arbitrarily and even though the statistical superiority of prucalopride was demonstrated in the three trials using this threshold, statistical significance alone was not sufficient to demonstrate the clinical relevance of the findings.[15] Additional psychometric analyses were needed to gain more detailed insights on the performance of the measurement instrument and the clinical meaning of its scores, and to confirm that the PAC-QOL is a valid scientific measure able to produce interpretable results in the prucalopride clinical trials.

Therefore, the objectives of this paper were to report the psychometric properties of the PAC-QOL in the pooled prucalopride trials populations, and to provide guidance for the interpretation of the clinical significance of the PAC-QOL scores, including the clarification of the meaning of a 1-point improvement.

MATERIALS AND METHODS

Study design

The three studies were conducted with the same study design: they were multicentre, randomized, double-blind, placebo-controlled, parallel-group, Phase III trials. They were conducted independently and patients could not be included in more than one of the three studies. Hence data from the three trials were pooled to perform the analysis reported here.

Two studies were conducted exclusively in the USA, while the third study was international (Australia, Europe, Canada, South Africa). Patients included in the studies were treated with prucalopride 2 mg, prucalopride 4 mg or placebo, given orally once daily for 12 weeks. The primary efficacy endpoint, i.e. the proportion of patients having on average ≥3 SCBM/week, was evaluated over the first 4 weeks of treatment and over the entire 12 weeks of therapy.

Health-related quality of life was assessed during the three trials by the PAC-QOL questionnaire, completed at baseline, week 4 and at the end of week 12. The PAC-QOL dissatisfaction score was prespecified in the clinical trial protocols as the primary PAC-QOL score of interest. In addition, subjects had to complete the Patient Assessment of Constipation Symptoms (PAC-SYM) severity index at each visit (i.e. baseline, week 2, week 4, week 8 and week 12),[16] the generic 36-item Short-Form questionnaire (SF-36) at baseline, week 4 and week 12,[17] a global evaluation of constipation severity at each visit of the trials, and a global evaluation of treatment efficacy at week 2, week 4, week 8 and week 12.

The three studies were conducted in accordance with the ICH Good Clinical Practice Guidelines, the Declaration of Helsinki and local laws and regulations. The clinical trial protocols were reviewed and approved by independent ethics committees and participants gave written informed consent.

Patients

Adult patients (≥18 years) of both genders with a history of chronic constipation [defined as having ≤2 spontaneous complete bowel movements (SCBM)/week for a minimum of 6 months before the selection visit] were eligible to enter the studies. Patients also had to show one or more of the following symptoms for at least one-quarter of the time: lumpy/hard stools, a sensation of incomplete evacuation, or straining during defecation. Patients were asked to record their bowel habits and movements in daily diaries during the 2-week, drug-free run-in phase to confirm the presence of their constipation. Patients were excluded if the constipation was drug-induced or secondary to endocrine, metabolic or neurological disorders, surgery, known or suspected organic disorders of the large intestine, or megacolon. Other exclusion criteria were uncontrolled cardiovascular, liver, and lung diseases, impaired renal

function (serum creatinine >180 μmol L^{-1}), and clinically significant abnormal laboratory values.

The PAC-QOL

The PAC-QOL is a self-administered questionnaire for the assessment of the magnitude and degree of interference associated with constipation symptomatology developed in conjunction with the PAC-SYM. The conceptual framework of the PAC instruments is based on the Wilson and Cleary model of health outcomes linking biological and physiological factors with patient-based symptoms, functioning, general health perceptions and overall quality of life.[18] The PAC-QOL is composed of 28 items grouped into four subscales related to dissatisfaction (5 items), physical discomfort (4 items), psychosocial discomfort (8 items), and worries and concerns (11 items). The overall and all subscale scores range from 0 to 4, with lower scores indicating better health-related quality of life. Validation studies conducted in the United States, Europe, Canada, and Australia have confirmed that the PAC-QOL is internally consistent, reproducible, valid, and responsive to improvements over time. Based on data from validation studies, half a point change, estimated with an anchor-based method using patients' self-rating of their global severity of constipation, is recommended as the minimum important difference (MID) for the overall PAC-QOL score.[19] To be conservative in the analysis of the Phase III trials, a 1-point improvement was chosen as the response to treatment.

Statistical analysis

All statistical analyses were performed on the pooled ITT population of the three prucalopride clinical trials, including all randomized subjects who took at least one dose of trial medication and who provided any follow-up data for one or more key efficacy variables.

Psychometric properties The psychometric properties of the PAC-QOL were first checked on baseline data. The quality of completion of the PAC-QOL was described to analyse the acceptability of the questionnaire by patients. A multi-trait analysis, analysing the correlation between each item and each subscale, was performed to check the relevance of item grouping into dimensions (known as construct validity). The internal consistency reliability of the PAC-QOL, i.e. the extent to which individual items within a dimension are consistent with each other and reflect a single underlying concept, was analysed using Cronbach's alpha statistic (the recommended threshold of satisfying reliability is alpha ≥0.70).[20] The concurrent validity, aiming at comparing scores of the questionnaire of interest with scores of a well-established questionnaire, was evaluated by analysing correlation coefficients between each PAC-QOL score and each SF-36 score, with the hypothesis that the PAC-QOL dissatisfaction score should have low-to-moderate correlation with SF-36 scores, as the SF-36 does not capture the very specific concept of satisfaction with bowel movements. The clinical validity, i.e. the ability of the scores to discriminate between patients with different clinical severity levels, was assessed by describing the mean PAC-QOL scores in patient groups with different levels of known severity of constipation (based on the percentage of subjects having at least 3 SCBM per week during the week 9–12 period, and on the PAC-SYM overall score at week 12). The responsiveness, referring to the ability of the scores to detect changes over time, was assessed between baseline and week 12 by comparing the change in PAC-QOL scores between patients who rated their treatment as extremely effective, quite a bit effective, moderately effective, a little bit effective and not at all effective at the end of week 12.

Guidance for interpretation To support the 1-point threshold used to define the response to treatment, the MID, corresponding to the minimal change in score that is perceived by patients as a benefit in the domain of interest,[21] was estimated to check that it was lower than 1 point. As there is no universally agreed method for calculating MID, the MID of each PAC-QOL score was estimated by using both anchor-based and distribution-based methods.[22] A first distribution-based method considers that a medium effect-size (ES), equal to 0.5 times the standard deviation (SD), is generally clinically significant.[23] A second distribution-based method considers that the MID corresponds to the Standard Error of Measurement (SEM)[24] calculated as $SD \times (1-r)^{1/2}$ where r is the reliability coefficient of the score. The MID was thus calculated as $0.5 \times SD$ of the baseline score, and using the SEM definition with the Cronbach's alpha of the score as reliability coefficient. The MIDs calculated using the anchor-based method were defined as the mean change in PAC-QOL scores observed for subjects showing a mild improvement in their evaluation of the severity of their constipation, ranging from 0 to 4 with 4 the highest severity, between baseline and week 12.

To evaluate whether a 1-point decrease (improvement) in PAC-QOL scores is clinically meaningful, the characteristics of subjects who improved in PAC-QOL scores by more than 1 point were compared to those who improved between 0 and 1 point, or who deteriorated.

To complete the main treatment effect analysis – which consisted of ANCOVA models with the change in score from baseline as the dependent variable, and the treatment, the baseline value of the score and the country as the independent variables – within- and between-group ES were calculated between baseline and week 12 and interpreted using Cohen's thresholds of 0.2, 0.5 and 0.8 for small, medium and large effects respectively.[25] Cumulative response curves, presenting the cumulative percentage of subjects reporting each possible PAC-QOL change in score observed for each treatment group, were drawn for each PAC-QOL change in score. An asymptotic Kolmogorov–Smirnov (KSa) test was used to compare the cumulative distribution of changes in PAC-QOL scores between treatment groups.

RESULTS

Patients from the three prucalopride trials populations reported similar characteristics at baseline in terms of age, gender, history of constipation, global evaluation of the severity of constipation and PAC-SYM overall score (Table 1), supporting the pooling of data from the three trials.

Psychometric properties of the PAC-QOL questionnaire

From the 1924 patients included in the pooled ITT population, a total of 1919 PAC-QOL questionnaires were available at baseline and 1630 at week 12. Less than 0.5% of missing data were observed per subject at baseline, and the percentage of missing data per item was lower than 0.7% for all items, except for 'Satisfied with your treatment?' which presented 5.6% of missing data. However, subjects had not yet taken the study treatment at baseline, explaining the difficulty for subjects to answer this item. The observed mean baseline score ranged from 1.2 for the psychosocial discomfort score to 3.3 for the dissatisfaction score, which also presented a ceiling effect with 20.6% of subjects having the highest possible score (i.e. 4). All items of the questionnaire except items 'Satisfied with your treatment?' and 'Felt in control of your situation?' presented a correlation with their own dimension higher than 0.4, and all items except item 'Had fewer bowel movements than you would like?' correlated more with their own dimension than with the other dimensions, confirming the relevance of the dimension structure of the PAC-QOL. Inter-dimension correlations ranged from 0.21 to 0.65 and all four dimensions were highly correlated with the overall score (between 0.54 with the dissatisfaction dimension and 0.93 with the worries and concerns dimension). Cronbach's alpha was greater than the recommended 0.70 threshold for all PAC-QOL dimensions, ranging from 0.77 for the dissatisfaction dimension to 0.94 for the 28 items-overall score. As expected, the dissatisfaction score was poorly correlated with all SF-36 scores, with correlation coefficients ranging from −0.01 to −0.18.

Table 1 Baseline characteristics of study population per trial

		Trial 1 (*N* = 713)	Trial 2 (*N* = 570)	Trial 3 (*N* = 641)	Total (*N* = 1924)
Country (%)	Australia	5.8	0.0	0.0	2.1
	Europe*	51.5	0.0	0.0	19.1
	Canada	27.8	0.0	0.0	10.3
	South Africa	15.0	0.0	0.0	5.6
	USA	0.0	100.0	100.0	62.9
Gender (%)	Female	90.7	88.1	86.6	88.6
Age (years)	Mean (SD)	44.0 (15.2)	48.7 (13.6)	48.0 (13.6)	46.7 (14.4)
	Minimum–Maximum	17.0–89.0	18.0–85.0	18.0–95.0	17.0–95.0
Duration of constipation (years)	Mean (SD)	17.6 (14.8)	21.3 (16.7)	22.0 (16.1)	20.2 (15.9)
	Minimum–Maximum	0.5–79.0	0.5–79.0	0.3–82.0	0.3–82.0
Number of spontaneous stools per week (%)	No spontaneous stool	38.6	37.7	44.0	40.1
	>0 and ≤1	32.4	38.4	31.8	34.0
	>1 and ≤3	25.8	23.0	22.8	24.0
	>3	3.2	0.9	1.4	1.9
Subject's global evaluation of severity of constipation (%)	Absent	1.7	1.1	0.6	1.1
	Mild	6.2	4.7	4.1	5.0
	Moderate	31.4	35.8	34.6	33.8
	Severe	40.1	39.8	40.7	40.2
	Very severe	19.9	17.7	19.8	19.2
PAC-SYM overall score	Mean (SD)	2.1 (0.7)	1.9 (0.7)	2.0 (0.7)	2.0 (0.7)
	Minimum–Maximum	0.2–3.9	0.1–4.0	0.1–4.0	0.1–4.0

*Europe including Belgium, Great Britain, The Netherlands, Norway and Sweden.
PAC-SYM, patient assessment of constipation symptoms.

The other PAC-QOL scores presented moderate negative correlation coefficients (between −0.42 and −0.52) with some SF-36 scores (bodily pain, mental health, vitality, and social functioning), indicating close but not redundant concepts measured by the PAC-QOL and SF-36 scores. All PAC-QOL scores at week 12 were lower (i.e. better) for subjects who presented at least 3 SCBM per week during the week 9–12 period as compared to those who did not, with differences in mean dissatisfaction, physical discomfort, psychosocial discomfort, worries and concerns, and overall scores of 1.48, 1.04, 0.54, 0.89, and 0.92 points respectively. The clinical validity of the PAC-QOL scores was also confirmed by an increase in all PAC-QOL scores together with the increase in severity of constipation-related symptoms as measured by the PAC-SYM overall score (Fig. 1).

Responsiveness of the PAC-QOL was confirmed through the highest improvements in all PAC-QOL scores being observed for subjects rating their treatment as extremely effective, and the lowest improvements being observed for subjects rating their treatment as not effective (Fig. 2). The most responsive score was the dissatisfaction score for which the greatest differences between groups of subjects were observed. Subjects evaluating their treatment as extremely effective reported an improvement of more than 2 points in their dissatisfaction score while a deterioration in dissatisfaction score was observed for subjects evaluating their treatment as not effective.

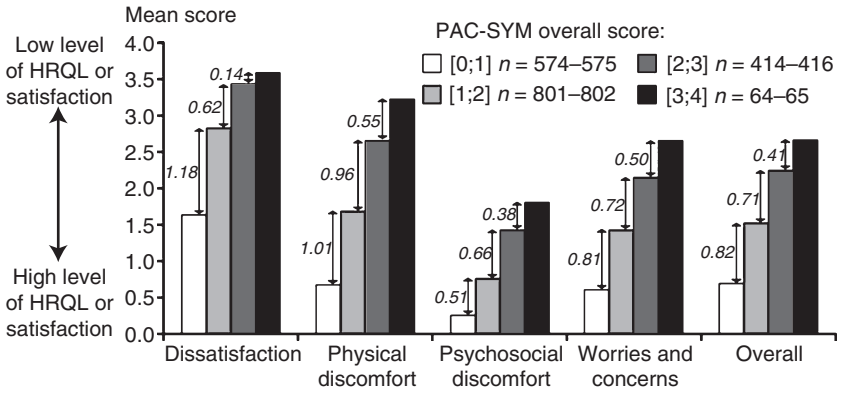
Guidance for interpretation of PAC-QOL scores

Even though distribution-based and anchor-based methods resulted in various MIDs, all estimated MIDs were lower than 1. Minimum important differences calculated as 0.5 × SD ranged from 0.36 for the dissatisfaction and overall scores to 0.48 for the worries and concerns score (Table 2), while MIDs calculated as the SEM were lower, ranging from 0.19 for the overall score to 0.38 for the physical discomfort score. Minimum important differences calculated using anchor-based method tended to be higher than those calculated using distribution-based methods, ranging from 0.48 for the psychosocial discomfort score to 0.88 for the physical discomfort score.

Compared to subjects with an improvement of less than 1 point or with a deterioration in PAC-QOL overall score, subjects with an improvement of more than 1 point showed the greatest improvement in the severity of constipation (−1.6 point for a scale ranging from 0 to 4 with 4 the highest severity) and a majority of subjects evaluating their treatment as 'Quite a bit' or 'Extremely' effective (41% and 25% respectively). These subjects also reported the greatest improvement in the severity of symptoms assessed by the change in PAC-SYM overall score (−1.3 point for a score ranging from 0 to 4 with 4 the greatest problems with symptoms) and the highest percentage of subjects with at least 3 SCBM per week during the week 1–12 period (40%) (Table 3). Similar results were observed for the subjects with an improvement greater than 1 point in the other PAC-QOL scores.

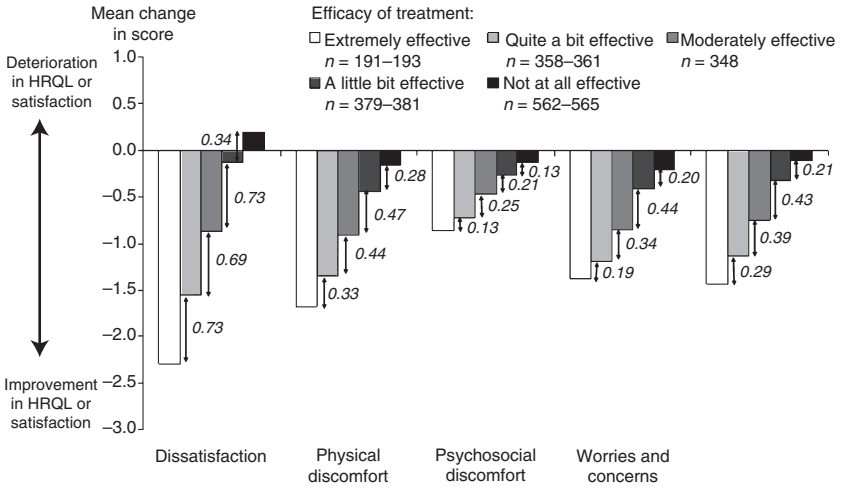
Treatment effect analysis

Both prucalopride and placebo groups presented an improvement in all PAC-QOL scores (Table 4). However, within-group ES indicated a large improvement (ranging from −0.80 to −1.17) for subjects treated with



Global differences in mean scores between groups significant [*P*(Kruskall-Wallis) < 0.0001].
In italics, difference in mean score between the 2 adjacent subgroups.
PAC-SYM overall score range from 0 to 4, with 4 being the highest problems with symptoms

Figure 1 Clinical validity of the PAC-QOL: comparison of week 12 PAC-QOL scores by severity of constipation-related symptoms as measured by the PAC-SYM overall score.



Global differences in mean change in scores between groups significant [*P*(Kruskall-Wallis) < 0.0001].
In italics, difference in mean change in score between the 2 adjacent subgroups.

Figure 2 Responsiveness of the PAC-QOL: comparison of PAC-QOL changes in scores from baseline to week 12 by efficacy of treatment as evaluated by subjects at week 12.

prucalopride 2 mg and 4 mg, except for the psychosocial discomfort subscale score, whereas within-group ES indicated a small-to-medium improvement (ranging from −0.36 to −0.61) for all PAC-QOL scores in the placebo group. Differences in adjusted mean PAC-QOL change in scores compared to placebo were also in favour of both prucalopride 2 mg and 4 mg groups ($P < 0.001$ for all scores), with corresponding ES ranging from −0.14 for the psychosocial discomfort score to −0.78 for the dissatisfaction score.

The cumulative distribution curves of the patient dissatisfaction score, predefined as the primary PAC-QOL endpoint, clearly distinguished prucalopride 2 and 4 mg from placebo (Fig. 3). The percentage of responders in the prucalopride group was always higher than in the placebo group whatever the threshold level of improvement [P (KSa) < 0.05]. With a definition of response to treatment of 1-point improvement, 44% of responders were observed for both prucalopride groups, whereas 24% of responders were observed in the placebo group.

Similar results were observed for the other PAC-QOL scores (all P (KSa) < 0.05). With a definition of response to treatment as a 1-point improvement, differences in the percentage of responders between prucalopride and placebo groups were 6% for the psychosocial discomfort score, 16% for the physical discomfort score, 16% for the worries and concerns score and about 15% for the total score.

Table 2 Minimal important differences estimated using distribution-based and anchor-based methods

Dimension	Distribution-based methods		Anchor-based method*
	0.5 × SD	SEM	
Dissatisfaction	0.36	0.35	0.80
Physical discomfort	0.43	0.38	0.88
Psychosocial discomfort	0.45	0.34	0.48
Worries and concerns	0.48	0.27	0.79
Overall	0.36	0.19	0.72

*MID corresponding to the mean change in score for subjects with a mild improvement in their evaluation of the severity of constipation between baseline and week 12.
MID, Minimal important difference.

DISCUSSION

The evaluation of the psychometric properties of the PAC-QOL in the prucalopride trials population confirmed its internal consistency reliability, validity and responsiveness to measure the impact of chronic constipation symptoms on health-related quality of life. The mean PAC-QOL scores were similar between the original US validation study and the baseline assessment of prucalopride trials (e.g. 0.9 in the validation study and 1.2 in the prucalopride trials for psychosocial discomfort dimension; 3.5 in the validation study and 3.3 in the prucalopride trials for dissatisfaction dimension). Results of the construct validity and internal consistency reliability were also similar between the two studies. In the US validation study, the clinical validity of PAC-QOL scores was demonstrated according to abdominal pain reported by patients and investigator and patient global ratings but could not be demonstrated according to the bowel movement frequency. In contrast, a significant relationship was shown in the prucalopride population between PAC-QOL scores and both severity of consti-

Table 3 Clinical meaningfulness of 1-point decrease (improvement) in PAC-QOL overall score between baseline and week 12

	Change in PAC-QOL overall score between BL and week 12		
	Improvement >1 point (n = 521)	Improvement between 0 and 1 point (n = 944)	Worsening (n = 386)
Change in global evaluation of constipation severity* between BL and week 12, Mean, SD	−1.6 (1.1)	−0.5 (1.0)	0.3 (1.1)
Subjects' global evaluation of efficacy at week 12 (%)			
Not at all	4.6	34.9	**54.9**
A little bit	8.3	24.1	**28.5**
Moderately	**21.3**	21.1	9.8
Quite a bit	**40.9**	14.1	3.9
Extremely	**25.0**	5.6	2.6
Change in PAC-SYM overall score** between BL and week 12, Mean, SD	**−1.3 (0.7)**	−0.4 (0.6)	0.1 (0.6)
Patients with ≥3 SCBM/week during the week 1–12 period (%)	**39.9%**	16.3%	8.0%

All differences in mean change and in percentage between the three groups significant [P (Kruskall-Wallis) and P (chi-square) <0.0001].
In bold, highest mean change or highest percentage between the three groups.
*Global evaluation of constipation severity score ranges from 0 to 4, with 4 being the highest severity.
**PAC-SYM overall score ranges from 0 to 4, with 4 being the highest problems with symptoms.
BL, baseline.

pation-related symptoms as measured by the PAC-SYM overall score and bowel movement frequency, indicating that patients' perception of constipation clearly depended on the bowel movement frequency in this study. This result was surprising as constipated patients often complain more about symptoms than about the poor frequency of defecations per week. The dissatisfaction score, that demonstrated the greatest

Table 4 Adjusted mean PAC-QOL changes in scores from baseline and difference in adjusted mean PAC-QOL changes in scores *vs* placebo, within-group and between-group ES

		Within-group changes in scores		Changes in scores *vs* placebo	
PAC-QOL	Treatment group	Adjusted mean change	Within-group ES	Difference in adjusted mean change	Between-group ES
Dissatisfaction	Placebo	−0.31	−0.46		
	Prucalopride 2 mg	−0.85	**−1.17**	−0.54	**−0.76**
	Prucalopride 4 mg	−0.87	**−1.15**	−0.56	**−0.78**
Physical discomfort	Placebo	−0.51	−0.61		
	Prucalopride 2 mg	−0.90	**−1.08**	−0.39	−0.47
	Prucalopride 4 mg	−0.84	**−0.96**	−0.33	−0.38
Psychosocial discomfort	Placebo	−0.32	−0.36		
	Prucalopride 2 mg	−0.48	−0.55	−0.16	−0.18
	Prucalopride 4 mg	−0.45	−0.53	−0.13	−0.14
Worries and concerns	Placebo	−0.45	−0.47		
	Prucalopride 2 mg	−0.82	**−0.87**	−0.37	−0.38
	Prucalopride 4 mg	−0.78	**−0.80**	−0.33	−0.34
Overall	Placebo	−0.40	−0.55		
	Prucalopride 2 mg	−0.74	**−1.04**	−0.34	−0.47
	Prucalopride 4 mg	−0.71	**−0.98**	−0.31	−0.42

All adjusted mean changes in scores and differences in adjusted mean changes in scores significantly different from 0 [P (ANCOVA) < 0.001].
In bold, ES reflecting a large change in score or difference *vs* placebo.
ES, effect-sizes.

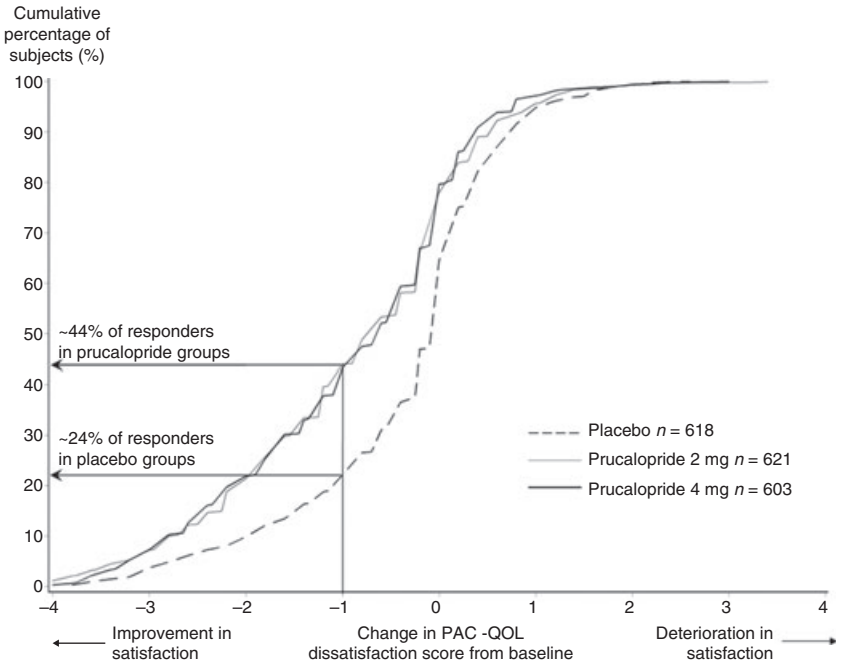


Figure 3 Cumulative response curve of the change in PAC-QOL dissatisfaction score between baseline and week 12.

improvement during the US validation study, was also found to be the most responsive PAC-QOL score in the prucalopride trial population. The PAC-QOL could therefore be considered as a good measure of health-related quality of life of constipated patients in the prucalopride trials.

Nevertheless, one limitation of the psychometric part of this study is that the test-retest reliability of the PAC-QOL, referring to the extent to which the measure yields the same results in repeated applications in an unchanged population, was not evaluated because of the study design of the prucalopride trials. In our study, it was difficult to define an unchanged population as patients were treated by either prucalopride or placebo which can also impact patients' quality of life and satisfaction with their bowel function and treatment.

Results of the main treatment effect analysis of the PAC-QOL questionnaire showed a significant improvement in all PAC-QOL scores when treated with prucalopride as compared to placebo, and this was consistent over the three trials.[11–13] However, these main results which were analysed using ANCOVA models may be difficult to interpret because they are only presented in terms of mean treatment group changes in scores and their associated *P* value. The meaningfulness of such mean change in scores is often unclear as statistical significance is known to be insufficient when interpreting patient-reported outcomes.[15] The use of effect-sizes can be useful to interpret treatment effect findings. In our study, the within-group treatment effect calculated for each treatment group showed PAC-QOL effect-sizes close to 1 (interpreted as large improvement) for both prucalopride 2 mg and 4 mg groups, except for the psychosocial discomfort score (interpreted as moderate improvement), but small-to-moderate effect-sizes for the placebo group. The between-group differences were also in favour of prucalopride, with effect-sizes ranging from small for the psychosocial score to large for the dissatisfaction score. However, effect-sizes remain a statistical summary of the treatment effect at the group level. In addition, effect-sizes depend on the sample size, i.e. the larger the sample size, the lower the variability of the score and the higher the effect-sizes. With more than 600 subjects per treatment group, one could argue that the large effect-sizes observed, in particular for the dissatisfaction score, may not be conclusive. Such group level analysis may not necessarily represent the change in score that is perceived as beneficial by the individual patient and provides no information on the proportion of patients who benefit from treatment.

This is the reason why the proportion of patients who benefited from treatment (also called analysis of responders by Patrick *et al.*[26]) was calculated for the three individual prucalopride trials, with a target response level of 1-point improvement in PAC-QOL scores. To support this 1-point threshold, we calculated MID that were all lower than 0.5 when using distribution-based methods, and lower than 0.9 when using an anchor-based method, indicating that a 1-point difference is a relevant definition of response for treatment group comparisons. The majority of subjects with more

than 1-point of improvement in PAC-QOL scores were consistently improved compared to those not reaching this level of improvement on different clinical criteria of severity of constipation and efficacy of treatment. This again indicated that a 1-point improvement is a relevant response criterion. It is also interesting to note that for the prucalopride group, the percentage of responders defined by a 1-point improvement on the PAC-QOL dissatisfaction endpoint (44%) was consistently higher than the corresponding bowel frequency based responder rate (ranging from 19.5% to 30.9%).[11–13]

Our attempt to calculate MID estimates showed the difficulty of this exercise, as the different methods we used provided different results. This variability in the estimation of MID reflects the complexity of defining a single point that could be used to compare treatment groups, even though the 1-point threshold for a 0–4 range used in the prucalopride trials was conservative and proved to be relevant. Cumulative distribution curves provide more complete information than only one specific MID between-groups point estimate, as they show the full pattern of response over time and therefore enable the entire distribution of response to be compared between treatment groups. For these reasons, cumulative distribution curves rather than MID criteria have recently been recommended by the FDA to demonstrate effect of treatment on patient-reported outcomes endpoints.[26] Cumulative distribution curves of PAC-QOL changes in scores showed consistent superior effects of prucalopride to placebo across the entire distribution of the scores.

In conclusion, the PAC-QOL is a constipation-specific instrument measuring patients' health-related quality of life and satisfaction, with demonstrated adequate psychometric properties. A 1-point improvement in PAC-QOL scores was found to be clinically relevant as the majority of subjects reaching this 1-point improvement threshold also had an improvement in bowel movement frequency. Cumulative distribution curves helped interpret the difference between treatment groups by confirming the superiority of prucalopride over placebo across the entire distribution of PAC-QOL changes in scores. Finally, by directly reflecting the patient's own perspective on constipation and its treatment, the PAC-QOL adds a useful patient-reported outcomes assessment tool for use in future clinical trials and eventually also for informing daily medical practice.

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