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RESEARCH ARTICLE

Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: Findings from the EXTEND study

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Abstract

Patients with persistent/chronic immune thrombocytopenia (cITP) have low platelet counts, increased risk of bleeding and bruising, and often suffer from reduced health-related quality of life (HRQoL). cITP treatments may either improve HRQoL by increasing platelet counts or decrease it because of side effects. The open-label EXTEND study (June 2006 to July 2015) evaluated long-term safety, tolerability, and efficacy of eltrombopag (an oral thrombopoietin-receptor-agonist) in adults with cITP who completed a previous eltrombopag ITP trial. The final results of EXTEND were published and used to assess changes in patient-reported HRQoL over time and association between HRQoL and platelet response. Four validated HRQoL instruments were administered: SF-36v2 including physical component summary (PCS) and Mental Component Summary; Motivation and Energy Inventory Short Form (MEI-SF); Fatigue Subscale of FACIT (FACIT-Fatigue); and FACT-Thrombocytopenia Subscale Six-Item Extract (FACT-Th6). For the 302 patients enrolled, median duration of eltrombopag treatment was 2.37 years. All 4 HRQoL instruments demonstrated positive mean changes from baseline over time adjusted for patient baseline characteristics and rescue therapy use, and had positive association with platelet response (platelet count ≥30 × 10^9/L; ≥50 × 10^9/L; and ≥50 × 10^9/L and >2 times baseline). Improvements from baseline started within 3 months and persisted through 5 years of treatment for FACIT-Fatigue and FACT-Th6 (P <.05 for nearly all time points); through 2.5 years for SF-36v2 PCS and less consistently for the MEI-SF. In conclusion, in addition to eltrombopag increasing platelet counts and reducing bleeding/bruising, it also alleviated fatigue, concerns about bleeding and bruising, and improved physical function in many patients, especially responders.

KEYWORDS

bleeding, fatigue, platelets, thrombopoietin receptor agonist, vitality

1 | INTRODUCTION

Persistent and chronic immune thrombocytopenia (cITP) are autoimmune disorders of duration 3-12 months or more than 12 months, respectively, with platelet count <100 × 10^9/L arising from autoantibody and T cell-mediated increased platelet destruction and reduced platelet production.[1] cITP occurs primarily in adults because children with ITP have a much higher rate of spontaneous remission. The prevalence of cITP in the United States (US) increases with age, and is uncertainly estimated to be 5.6-20 per 100 000 adults, based on the 2005 census population.[2] A 2009 review of studies conducted in Denmark, Sweden, and the United Kingdom estimated the incidence of ITP to be 3.3 per 100 000 adults[3] and a separate study in 2011 reported ITP incidence of 2.20 per 100 000 adults in Japan.[4]

The most common hematologic symptoms of ITP include bruising and skin-mucosal bleeding, particularly of the mouth and nose. ITP is also

commonly associated with fatigue and fear of bleeding that can interfere with daily activities. Complications due to bleeding are more common in patients with platelet counts <30 × 10^9/L, thus, published guidelines recommend ITP treatment initiation in adults when platelet counts fall below 30 × 10^9/L.[5–7] Treatment of ITP is intended to increase platelet counts to a hemostatic range to decrease the risk of bleeding; it also seeks to ameliorate the associated reductions in health-related quality of life (HRQoL).

In the past decade, studies have unequivocally demonstrated the substantial impact of cITP on HRQoL. In the first ITP study of HRQoL, scores in adult patients with cITP were not only lower than scores in the general US population, indicating poorer HRQoL, but were also lower than reported HRQoL scores in patients with certain other chronic conditions including hypertension and arthritis.[8] Bleeding episodes and fear of bleeding, unexplained fatigue, nonspecific aches and pains, decreased emotional health, low energy/depression, decreased desire to socialize, and reproductive health issues in men and women including erectile dysfunction and menorrhagia have all been cited as reasons for lower HRQoL scores in patients with cITP.[9,10]

ITP focus groups reported significant impairments in overall HRQoL as described above and reported that reduced HRQoL was due to not only the disease but also side effects associated with its treatment. The most common treatment-related adverse effects were those associated with corticosteroids, the mainstay of ITP therapy, including weight gain, mood swings, anger, and insomnia, and were particularly emphasized as negatively affecting HRQoL.[10] In a survey of over 500 patients with ITP, more than 50% of patients reported feeling "highly bothered" by corticosteroid-induced symptoms.[11] Adverse effects of intravenous immunoglobulin, antiD immunoglobulin, and rituximab therapy have also been reported to have side effects reducing HRQoL.[12]

Eltrombopag is an oral thrombopoietin-receptor-agonist approved for the treatment of cITP in adults and children over the age of 1 year who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[13–16] Eltrombopag stimulates platelet production by binding to the transmembrane domain of the thrombopoietin receptor and inducing proliferation and differentiation of megakaryocytes.[17,18] Studies have shown that treatment with eltrombopag often increases platelet counts and is generally well-tolerated by healthy volunteers and patients with cITP, thrombocytopenia caused by hepatitis C-related cirrhosis, and severe aplastic anemia.[13,14,19,20] Increases in platelet counts with long-term treatment with eltrombopag reduce not only the number of bleeding events, but also the need for concomitant and rescue medications.[14] Given the efficacy of eltrombopag in long-term treatment of cITP in EXTEND (Eltrombopag Extended Dosing Study), this analysis explored the effects on HRQoL with continuing eltrombopag treatment. The specific objectives of this study were to assess: (*a*) changes from baseline over time in patient-reported HRQoL in all patients and (*b*) the association between patient-reported HRQoL and platelet response.

2 | METHODS

2.1 | Study design and patient selection

EXTEND (June 2006 to July 2015) was an open-label, single-arm, dose-adjustment, multi-national extension study (ClinicalTrials.gov identifier: NCT00351468) that evaluated safety and efficacy of eltrombopag as a treatment for patients aged 18 years or older with ITP of at least 6 months duration who had participated in previous eltrombopag trials (during which they could have received either eltrombopag or placebo). At the initiation of EXTEND, cITP was defined as ITP lasting at least 6 months.[5,21,22] EXTEND consisted of four stages:

1. Eltrombopag was initiated at 50 mg once daily and adjusted to attempt to increase platelets to ≥100 × 10^9/L.
2. For the approximately one-third (33.4%) of patients receiving concomitant ITP medications, after an initial platelet increase, these concomitant ITP medications were reduced as possible while maintaining platelets ≥50 × 10^9/L.
3. For the same approximately one-third (33.4%) of patients receiving concomitant ITP medications, eltrombopag doses were adjusted between 75 and 25 mg daily or less frequently, to identify the minimal dose of eltrombopag necessary to maintain platelets ≥50 × 10^9/L, in conjunction with the minimal dose (including cessation) of concomitant ITP medication.
4. Long-term safety and efficacy of eltrombopag were then assessed at a dose maintaining platelet counts ≥50 × 10^9/L (when possible), in conjunction with the minimal dose of any concomitant ITP medication (if required).

Platelet counts were assessed weekly during the first 4 weeks, after any dose change, and every 4 weeks throughout the study. Patients whose platelet counts did not reach the 50 × 10^9/L threshold were permitted to continue treatment as long as they received benefit and did not experience more than moderate side effects. Willing, responding subjects who did not experience serious side effects and continued to require eltrombopag treatment continued in the study until either eltrombopag became commercially available to them, or a regulatory/reimbursement decision was made (eg, they were switched to commercial eltrombopag or another treatment).

Patient-reported HRQoL was prospectively and longitudinally assessed during long-term eltrombopag treatment in patients with persistent/cITP. Patients were included in the current HRQoL analyses if they had received at least 1 dose of eltrombopag and completed both a baseline assessment of HRQoL and at least one postbaseline assessment in order to assess change in HRQoL.

2.2 | Outcomes and covariates

Four HRQoL instruments were used in this study to assess change in HRQoL from baseline as secondary outcomes for EXTEND. The choice of instruments was based on the suggestions of ITP focus group participants that these questions/questionnaires capture unique aspects of ITP, fatigue, and the impact of bleeding and fatigue symptoms. HRQoL assessments were performed: at baseline; at the beginning of each stage; prior to any new intervention or change to therapy; and at a minimum frequency of every 3 months during a stage; and at withdrawal from eltrombopag. Patients were blinded to their current platelet count results before completing the questionnaires. The 4 HRQoL assessment tools were:

1. The acute recall version of the Medical Outcome Trust's Short-Form 36 Health Survey, Version 2 (SF-36v2) to measure general physical and mental health status.[23] SF-36v2 consists of 36 questions across 8 health domain scales (totaling to a summary scale of 0-100 with higher numbers indicating better HRQoL) and 2 health component summaries—the physical component summary (PCS) and the mental component summary (MCS). PCS and MCS scores were normalized, so that the 1998 US census general population has a mean = 50 and SD = 10, to allow for comparison of EXTEND study outcomes to that of the general population and/or of other chronic diseases.
2. Motivation and Energy Inventory-Short Form (MEI-SF) to measure motivation and energy.[24] 18 questions totaled to a summary scale from 0 to 108, where higher numbers indicate better motivation and energy HRQoL measures.
3. The fatigue subscale of the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue) to measure severity of fatigue across multiple dimensions and its impact on the patients' daily activities.[25] 13 questions were totaled to a summary scale from 0 to 52, where higher numbers indicate less fatigue and an increased ability to carry out daily activities.
4. The Functional Assessment of Cancer Therapy-Thrombocytopenia tool (FACT-Th6), a 6-item, patient-identified subset of questions from the FACT-Th, to measure concerns related to bleeding and bruising and their impact on usual activities.[26] Although the 6 items do not constitute a formal domain or subscale of the FACT-Th assessment tool, these items have been identified by focus groups of patients with cITP as important indicators of their HRQoL.[27] The FACT-Th6 was studied for comparative purposes in EXTEND and was not intended for development as a stand-alone instrument.[25] The 6 questions totaled to a summary scale from 0 to 24, in which higher numbers indicate better HRQoL measures.

Outcomes of interest included HRQoL change from baseline at different time periods, change in HRQoL from baseline to best post-baseline score, increase/improvement in HRQoL from baseline at least once during treatment with eltrombopag, and achievement of clinically meaningful increase in HRQoL from baseline based on minimally important differences (MIDs), on any of the four instruments and whether any changes persisted as treatment was continued. The MID can be defined as the smallest difference in score in the domain of interest which patients perceive as beneficial.[28] MIDs were calculated as a change from baseline summary score of at least one-half the SD[29] of the normalized scores (5 points) for SF-36v2 PCS and SF-36v2 MCS, at least one-half the SD of baseline scores observed across all patients for MEI-SF and FACT-Th6,[29] and at least 3 or 5 points for FACIT-Fatigue (as suggested by the literature[29]). The authors note while identifying clinical improvement with such a defined threshold may not always be precise, it is the "rule of thumb" to use one-half the SD of baseline values and this provides a consistent interpretation of HRQoL results. Changes in HRQoL summary scores equal to or exceeding the MID threshold were indicated to be clinically meaningful.

The potential association of HRQoL with platelet response was an additional secondary outcome in EXTEND. Three somewhat similar definitions of platelet response were identified, all in the absence of rescue therapy (defined as the use within 4 weeks of any of: new ITP medication, increase in dose of ITP medication from baseline, platelet transfusion, and splenectomy): (1) platelet count ≥30 × 10^9/L, (2) platelet count ≥50 × 10^9/L, and (3) platelet count ≥50 × 10^9/L and 2 times baseline.

2.3 | Statistical analysis

2.3.1 | Descriptive statistics

Demographic and clinical characteristics were assessed at baseline using means and SDs for continuous variables and frequencies and proportions for categorical variables. The proportion of patients with improvement (any increase) in HRQoL scores from baseline, the time to best improvement, and clinically meaningful changes based on MID were reported descriptively. Time to best HRQoL improvement and proportions of patients with a platelet response during different time intervals was graphed.

2.4 | Multivariate analysis

Multivariate analysis of change in HRQoL measures from baseline to different time periods was conducted for each instrument and domain using generalized estimating equations. HRQoL scores were calculated postbaseline to <3 months, ≥3 to <6 months, and at 6-month periods thereafter. The models adjusted for time period, baseline demographic and clinical characteristics (baseline use of cITP medication, prior splenectomy, prior exposure to eltrombopag, and baseline platelet count), and a time-varying covariate for rescue therapy use. Similar models were used for assessing best change in HRQoL. The covariates adjusted for baseline characteristics that may have been imbalanced across patients, given entry into this study from EXTEND may have been at different stages and treatment experiences. The models also adjusted for within-patient correlation.

Associations between HRQoL measures and each of the 3 definitions of platelet response over time were assessed longitudinally using generalized estimating equations. Mean platelet count based on clinical assessments and platelet response were calculated during time periods post-baseline to <3 months, ≥3 to <6 months, and at 6-month periods thereafter. Platelet response was determined among patients who had a platelet measurement in each interval, assessed for each response definition separately. The models adjusted for demographic and baseline clinical characteristics (BMI, baseline use of ITP medication, prior splenectomy, prior eltrombopag use, and baseline platelet count). A sensitivity analysis examined patients with baseline platelet counts <30 × 10^9/L (in certain studies there was no hiatus from the previous study to entry into EXTEND and therefore baseline platelet counts, while <30 × 10^9/L in the initial eltrombopag study, were >30 × 10^9/L upon entry into EXTEND).

3 | RESULTS

The final results of the EXTEND study have been published[30]; the HRQOL results discussed here are based on these final results. A total

TABLE 1 Adjusted mean best change from baseline for HRQoL instruments

HRQoL instrument	N[a]	Mean baseline score	Mean best change from baseline[b,c]	95% CI[d]	MID threshold
SF-36v2 (score range 0-100)					
Physical function	273	73.1	12.0	(9.6-14.5)	12.2
Physical role	273	67.1	14.2	(11.5-16.9)	13.5
Bodily pain	273	72.5	14.5	(11.6-17.4)	13.2
General health	273	52.5	11.1	(9.0-13.1)	10.9
Vitality	290	54.3	13.9	(11.6-16.3)	12.2
Social function	290	74.7	12.6	(10.2-15.1)	12.5
Emotional role	290	74.3	11.4	(8.7-14.0)	12.9
Mental health	290	68.4	11.3	(9.4-13.3)	10.1
PCS[e]	273	46.0	5.3	(4.5-6.2)	5.0
MCS[e]	290	45.5	5.8	(4.6-6.9)	5.0
MEI-SF (score range 0-108)	292	69.7	11.3	(9.1-13.5)	11.3
FACIT-Fatigue (score range 0-52)	291	35.5	6.9	(5.7-8.1)	3.0 or 5.0
FACT-Th6 (score range 0-24)	288	14.7	4.0	(3.4-4.6)	3.0

Abbreviations: CI, confidence interval; MID, minimally important difference.
[a] Number of patients with a baseline and at least one post-baseline HRQoL assessment and no missing covariate information.
[b] Positive change from baseline indicates HRQoL improvement.
[c] Generalized estimating equations were used to assess mean best change in HRQoL scores from baseline. The regression models adjusted for demographic and baseline clinical characteristics (BMI [SF-36v2 PCS and domains included in the PCS only] baseline platelet count, baseline use of ITP medication, prior exposure to eltrombopag, prior splenectomy) and indicator of rescue therapy use before best postbaseline score. Patients with missing covariates were excluded from the analyses (17 patients were excluded from the analyses of SF-36v2 PCS and domains included in the PCS due to missing baseline BMI score and 1 additional patient was excluded from all analyses due to another missing covariate).
[d] All *P*-values < .001.
[e] PCS and MCS scores were normalized so that the 1998 US census general population has a mean of 50 and SD of 10.

of 302 patients were enrolled in the EXTEND study between June 2006 and July 2015. Treatment duration per patient ranged from 2 days to 8.8 years with median treatment duration 2.4 years. Baseline platelet count was ≤15 × 10^9/L for 43.4% of patients, >15 to ≤30 × 10^9/L for 26.5%, >30 to <50 × 10^9/L for 17.2%, and ≥50 × 10^9/L for 12.9% of patients (those continuing eltrombopag from their previous study). The majority had prior exposure to eltrombopag (72.8%); 38.1% were splenectomized and 33.4% were treated with concomitant ITP medication at baseline. Additional baseline and demographic characteristics have previously been reported but are also shown in supplemental Table S1.[30]

3.1 | HRQoL at baseline

The number of patients who had a baseline and at least one on-treatment HRQoL assessment varied by instrument: 291 patients for SF-36v2, 293 for MEI-SF, 292 for FACIT-Fatigue, and 289 for FACT-Th6. The unadjusted mean ± SD SF-36v2 PCS and MCS scores at baseline were 46.1 ± 8.7 and 45.5 ± 11.7, respectively, slightly lower than the 50.0 ± 10.0 score of the general US population. The unadjusted mean baseline scores were 69.7 ± 22.5 for MEI-SF, 35.5 ± 12.1 for FACIT-Fatigue, and 14.7 ± 6.1 for FACT-Th6.

3.2 | Change in HRQoL measures from baseline to best postbaseline score

All HRQoL instruments had statistically positive, greater-than-MID-adjusted mean best changes from baseline (Table 1, all $P < .001$). Most patients experienced any improvement in HRQoL from baseline: 84.9% (SF-36v2 PCS); 82.8% (SF-36v2 MCS); 79.9% (MEI-SF); 77.1% (FACIT-Fatigue); and 80.6% (FACT-Th6). The median time to best improvement among patients who experienced improvement ranged from 6 to 10 months across different instruments. Median days to best improvement for each instrument were: 309.0 (SF-36v2 PCS), 285.0 (SF-36v2 MCS), 374.5 (MEI-SF), 276.0 (FACIT-Fatigue), and 183.0 (FACT-Th6) (Supporting Information Figure S1). Though most patients had HRQoL measures for at least 2 years, by 2.5 years, the sample of patients with measures had generally been reduced by half.

3.3 | Descriptive analysis of proportion of patients with HRQoL response from baseline

The proportions of patients achieving MID-exceeding clinically meaningful increases in HRQoL from baseline to different time periods for the different HRQoL instruments are illustrated in Supporting Information Figure S2. The proportions of patients achieving MID-exceeding clinically meaningful increases in HRQoL from baseline at least once during eltrombopag treatment were 49.5% for SF-36v2 PCS, 50.2% for SF-36v2 MCS, 48.1% for MEI-SF, 64.0% (3 points) and 51.0% (5 points) for FACIT-Fatigue, and 55.0% for FACT-Th6. Among the subset of patients who had at least 2 on-treatment assessments with HRQoL response (compared with baseline), and at least 6 months between the 2 on-treatment assessments, 46.2% (n = 119) of patients maintained HRQoL improvement for at least 6 months for SF-36v2 PCS, 53.4% (n = 118) for SF-36v2 MCS, 47.5% (n = 120) for MEI-SF, 60.9% (3 points, n = 161) and 63.4% (5 points, n = 131) for FACIT-Fatigue, and 62.4% (out of n = 133) for FACT-Th6.

TABLE 2 Adjusted mean change in FACIT-Fatigue, FACT-Th6, SF-36v2 PCS, SF-36v2 MCS, and MEI-SF over time compared with baseline

	SF-36v2 PCS (MID = 5.0)			SF-36v2 MCS (MID = 5.0)			MEI-SF (MID = 11.3)			FACIT-Fatigue (MID = 3.0 or 5.0)			FACT-Th6 (MID = 3.0)		
Time period	N[a]	Mean change[b]	*P*-value	N[a]	Mean change[b]	*P*-value	N[a]	Mean change[b]	*P*-value	N[a]	Mean change[b]	*P*-value	N[a]	Mean change[b]	*P*-value
>0 to <3 mo	231	1.5	<.001	231	1.1	.071	230	2.7	.015	231	2.1	<.001	228	2.1	<.001
≥3 to <6 mo	211	1.3	.007	211	0.4	.576	213	2.8	.020	211	2.0	.001	211	1.9	<.001
≥6 to <12 mo	228	1.7	<.001	228	0.2	.699	231	2.8	.024	228	2.6	<.001	225	1.8	<.001
≥1 to <1.5 years	208	1.3	.004	208	0.7	.244	208	2.1	.090	207	2.1	.002	203	2.1	<.001
≥1.5 to <2 years	182	1.6	.002	182	0.4	.575	185	3.4	.011	184	2.5	.001	180	2.1	<.001
≥2 to <2.5 years	161	1.1	.024	161	0.6	.401	162	2.7	.062	161	2.7	<.001	158	2.7	<.001
≥2.5 to <3 years	113	0.6	.344	113	−0.5	.560	115	1.1	.502	115	2.1	.014	113	2.3	<.001
≥3 to <3.5 years	95	1.2	.046	95	0.5	.565	96	0.8	.640	95	1.7	.072	93	2.3	<.001
≥3.5 to <4 years	80	0.6	.437	80	0.0	.968	80	0.9	.613	81	1.9	.038	78	2.1	<.001
≥4 to <4.5 years	66	1.3	.061	66	1.1	.225	66	3.2	.094	66	3.3	.002	66	2.4	<.001
≥4.5 to <5 years	55	0.4	.571	55	−0.7	.542	55	−1.1	.618	55	1.1	.290	52	2.4	<.001

CI = confidence interval.

[a] Estimates for follow up periods with less than 30 patients are not shown.

[b] Estimated mean score change from baseline (positive change indicates improvement). Generalized estimating equations were used to assess mean change in HRQoL scores from baseline to different time periods, accounting for within-patient correlation. The regression models adjusted for demographic and baseline clinical characteristics (BMI [SF-36v2 PCS only] baseline platelet count, baseline use of ITP medication, prior exposure to eltrombopag, prior splenectomy), and indicator of rescue therapy use during each time period. Patients with missing covariates were excluded from the analyses (17 patients were excluded from the analyses of SF-36v2 PCS due to missing baseline BMI score and 1 additional patient was excluded from all analyses due to another missing covariate). Estimates for time periods with less than 30 patients are not shown.

3.4 | Multivariate analysis of change in HRQoL measures from baseline to different time periods

All HRQoL instruments had positive adjusted mean changes from baseline over time starting at 0-3 months after baseline. Improvements from baseline persisted through 5 years of treatment for FACIT-Fatigue and FACT-Th6 (nearly all P <.05, Table 2). At 0-3 months after baseline the mean increase was 2.1 (70% of 3 point MID) for FACIT-Fatigue, and ranged from 1.1-3.3 to 5 years of treatment. At 0-3 months after baseline the mean increase was 2.1 for FACT-Th6 (69% of MID), and ranged from 1.8-2.7 through 5 years of treatment. The adjusted mean changes from baseline over time for FACIT-Fatigue and FACT-Th6 are also illustrated in Figure 1, as are those for the SF-36v2 PCS, SF-36v2 MCS, and MEI-SF, which had positive changes from baseline through 2.5 years. The Physical Function and General Health domains of the PCS contributed to this trend most strongly. The MEI-SF adjusted mean changes from baseline scores were generally positive and most sensitive within the first 2.5 years.

3.5 | Association between HRQoL measure and platelet response over time

As reported by Wong et al.,[30] 259 of 302 patients (85.8%) achieved a platelet count ≥50 × 10^9/L, and 276 of 302 patients (91.4%) achieved a platelet count ≥30 × 10^9/L, at least once in the absence of rescue therapy. Of the patients achieving a count ≥50 × 10^9/L, half of those eligible (133/257; 51.8%) had a continuous platelet count of ≥50 × 10^9/L or twice baseline for at least 25 weeks in the absence of rescue therapy, and 183/257 patients (71.2%) achieved a continuous platelet count ≥30 × 10^9/L in the absence of rescue therapy over the same period. All HRQoL instruments were positively associated with platelet response over time, and the SF-36v2 PCS, FACIT-Fatigue and FACT-Th6 were the most sensitive measures (P <.05) with significant associations for all definitions of platelet response (Table 3). The adjusted mean score difference between patients with platelet response in a given time interval and patients with no response (positive difference signifying better HRQoL with platelet response) was 0.9-1.3 for SF-36v2 PCS, 0.8-1.3 for SF-36v2 MCS, 1.3-1.9 for MEI-SF, 1.6-2.0 for FACIT-Fatigue, and 1.8-2.3 for FACT-Th6 (most P <.05). In the sensitivity analysis for patients with baseline platelet counts <30 × 10^9/L, HRQoL scores were also positively associated with platelet response.

4 | DISCUSSION

This study found positive mean changes in HRQoL scores from baseline during long-term treatment with eltrombopag for adults with persistent/cITP starting within 3 months after baseline. In particular, for HRQoL measures relating to fatigue and concerns about bleeding and bruising and their impact on usual activities, improvements persisted through 5 years and for those relating to physical health, improvements persisted through 2.5 years emphasizing the consistency of these effects. About 80% of patients with persistent/cITP

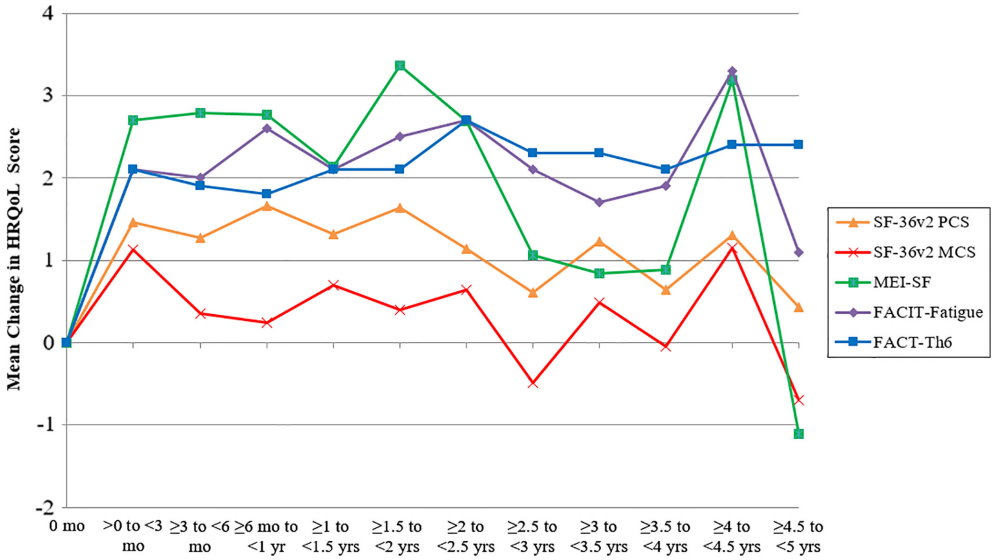

FIGURE 1 Estimated mean score change from baseline (positive change indicates improvement). Generalized estimating equations were used to assess mean change from baseline to different time periods, accounting for within-patient correlation. The regression models adjusted for demographic and baseline clinical characteristics (BMI [SF-36v2 PCS only] baseline platelet count, baseline use of ITP medication, prior exposure to eltrombopag, prior splenectomy), and indicator of rescue therapy use during each time period. Estimates for time periods with <30 patients are not shown. The number of patients decreases over time from 228 to 230 patients within 3 months from baseline to 52-55 patients from 4.5 to <5 years from baseline; the number of patients in each time period for each HRQoL instrument is shown in Table 2

treated with eltrombopag experienced an improvement from baseline in HRQoL at least once, with best improvement occurring most commonly within a year after baseline. In total 50%-64 % of patients achieved MID-exceeding clinically meaningful increases in HRQoL from baseline at least once during eltromobopag treatment. MID-exceeding HRQoL improvement was maintained for at least 6 months in 50%-60% of the patients who achieved it once. These findings are conservative given the natural attenuation of perception of benefit with time, the numbers available to evaluate durability at any point in time during the trial, and the less frequent and lower number of assessments over time. However, these results nonetheless demonstrate the positive association of eltrombopag treatment with improved HRQoL over time.

In the present study, baseline HRQoL of patients with persistent/cITP, as measured by the SF-36v2 instrument, was less than that of the general US population; however, it was similar to scores observed in prior trials of eltrombopag and romiplostim, a peptibody and thrombopoietic agent, and other ITP cohorts.[8,31,32] Baseline SF-36v2 and FACIT-Fatigue scores were consistent with shorter-term eltrombopag studies, reflecting impaired HRQoL in cITP patients compared with the general population.[23,25] Romiplostim has had similar platelet effects in cITP and also demonstrated improvements in HRQoL.[33] Mean baseline scores for each of the instruments in the current study ranged from one-half to three-quarters of the full scale, suggesting that having ITP negatively affects HRQoL in many ways as evidenced by various measures.

The positive mean changes in HRQoL from baseline started with assessments within 3 months and persisted through 5 years of treatment for FACIT-Fatigue and FACT-Th6 and through 2.5 years for SF-36v2 PCS. One-fourth to one-third of patients achieved their best improvement in the HRQoL instruments within 90 days of starting eltrombopag, and half achieved their best improvement within one year of starting therapy. There was a high degree of consistency among the HRQoL tools in median days to best improvement. Achieving best improvement within a year of starting therapy is consistent with the staging design of the clinical trial, in which tapering of concomitant medications like prednisone could be delayed for several months.

Each of the HRQoL domains and scores used in this study measures some dimension of fatigue, either the symptom itself or its physical and functional impact. As in previous studies of eltrombopag from 6 weeks to 6 months in duration, treatment with eltrombopag was often associated with consistent improvement in HRQoL scores across various domains related to fatigue and physical aspects of HRQoL, suggesting that eltrombopag therapy in patients may be associated with a persisting reduction in fatigue and its impact.[13,14,19,34]

While the current study found overall positive mean changes in HRQoL from baseline, HRQoL scores did not change or deteriorated for some patients (15.1% for SF-36v2 PCS; 17.2% for SF-36v2 MCS; 20.1% for MEI-SF; 22.9% for FACIT-Fatigue; and 19.4% for FACT-Th6).

Most patients achieved a platelet response as identified through at least one measure of their platelets during the follow-up period meeting the outcome definitions: 86.8% of patients achieved platelet count ≥30 × 10^9/L and 75.2% achieved ≥50 × 10^9/L and 2 times baseline. During the long-term eltrombopag therapy in the EXTEND study, platelet counts increased, bleeding symptoms (World Health Organization grades 1-4) decreased from 56.6% (171/302 patients) at baseline to 16.3% (13/80) at 1 year, and 33.7% (34/101) of patients with concomitant ITP use at baseline permanently stopped one or more concomitant ITP medication (most commonly corticosteroids).[30] Furthermore many patients with platelet response to eltrombopag had a consistent response. The effect of long-term treatment with eltrombopag on HRQoL may be both physiological (as increased

TABLE 3 Adjusted mean HRQoL score changes associated with platelet response in the absence of rescue therapy

	SF-36v2 PCS (score range: 0–100) (MID = 5.0) (*N* = 273)		SF-36v2 MCS (score range: 0-100) (MID = 5.0) (*N* = 290)		MEI-SF (score range: 0–108) (MID = 11.3) (*N* = 292)		FACIT-Fatigue (score range: 0-52)(MID = 3.0 or 5.0) (*N* = 291)		FACT-Th6 (score range: 0-24)(MID = 3.0) (*N* = 288)	
Platelet response	**Mean change[a]**	***P*-value**	**Mean change[a]**	***P*-value**	**Mean change[a]**	***P*-value**	**Mean change[a]**	***P*-value**	**Mean change[a]**	***P*-value**
Platelet count ≥30 × 10^9/L (ref: Platelet count <30 × 10^9/L)	1.3	<.001	1.3	.014	1.9	.048	2.0	<.001	2.3	<.001
Platelet count ≥50 × 10^9/L (ref: Platelet count <50 × 10^9/L)	0.9	.011	0.8	.083	1.3	.095	1.6	.001	2.0	<.001
Platelet count ≥50 × 10^9/L and 2× baseline (ref: Platelet count not meeting response definition)	1.0	.002	0.9	.055	1.9	.012	1.6	<.001	1.8	<.001
	Sensitivity analysis: Among patients with baseline platelet count < 30 × 10^9/L									
	(*N* = 193)		**(*N* = 201)**		**(*N* = 203)**		**(*N* = 202)**		**(*N* = 199)**	
Platelet count ≥30 × 10^9/L (ref: Platelet count <30 × 10^9/L)	1.3	.001	1.3	.015	1.9	.060	2.0	<.001	2.3	<.001
Platelet count ≥50 × 10^9/L (ref: Platelet count <50 × 10^9/L)	1.1	.011	1.0	.087	1.3	.143	1.5	.008	1.9	<.001
Platelet count ≥50 × 10^9/L and 2× baseline (ref: Platelet count not meeting response definition)	1.1	.007	0.9	.096	1.2	.185	1.5	.009	1.8	<.001

[a] Estimated mean HRQoL score difference with platelet response compared with no response in a time period. Positive changes indicate HRQoL improvement associated with platelet response. Generalized estimating equations were used to assess the association between HRQoL and platelet response over time, accounting for within-patient correlation. Other covariates included demographic characteristics and baseline clinical characteristics (BMI [for SF-36v2 PCS only], baseline platelet count, baseline use of ITP medication, prior splenectomy, and prior eltrombopag use. Patients with missing covariates were excluded from the analyses (17 patients were excluded from the analyses of SF-36v2 PCS due to missing baseline BMI score and 1 additional patient was excluded from all analyses due to another missing covariate).

platelet counts and reduction of bleeding and bruising can lead to less fatigue and improved physical health) and psychological (eg, less concerns about bleeding and their impact on usual activities).

Patient-reported HRQoL was positively associated with platelet response using multiple definitions of platelet response and persisted in the sensitivity analysis among patients with platelet count <30 × 10^9/L at baseline. Numerically the mean difference in HRQoL for patients with platelet response compared with patients without platelet response in a time period was higher when platelet response was defined as platelet count ≥30 × 10^9/L than when defined as platelet count ≥50 × 10^9/L. One possible explanation is that a threshold of platelet count ≥30 × 10^9/L is more clinically meaningful to patients, but this finding may also be due to having many patients with platelet counts near 50 × 10^9/L, which will result in a smaller differences in HRQoL when comparing HRQoL of patients with platelet count ≥50 × 10^9/L and <50 × 10^9/L.

Patient-reported outcomes are particularly meaningful, as they offer investigators the opportunity to garner patient perspectives on treatment efficacy: "the whole patient approach". Additionally, while the adjusted mean change in HRQoL associated with platelet response were below MID thresholds based on the multivariate model estimates, examining unadjusted changes would not have been appropriate. Using the adjusted change is a more conservative approach as differences in patient baseline and clinical characteristics, which explain some of the variation in HRQoL, are adjusted for. Results of this form of assessment suggest durable improvements in various HRQoL domains. These findings therefore demonstrate that persistent use of eltrombopag and its role in increasing platelet count can be reflected in the associated improvement in HRQoL in a substantial fraction of responding patients.

5 | LIMITATIONS

There are important limitations to this study. The first is the difficulty in identifying which measurements of HRQoL are most important or relevant, either to patients or their clinicians. In this study, however, multiple instruments, based on the suggestions of ITP focus group participants that these questionnaires and items capture unique aspects of ITP and their positive associations with platelet response (using multiple definitions of platelet response), are reassuring in this regard. This study was conducted before development of the BAT and the ITP-PAQ was unavailable for use in this study.

Second, in this long-term study, the number of patients remaining in the trial decreased over time and not all patients completed serial HRQoL assessments. Clear improvements in HRQoL could be seen immediately after baseline, as the sample size was largest at this time. However, after longer time periods near the end of the study, there were too few patients with HRQoL assessments to determine an effect. It is very possible that patients who left the trial were doing less well with treatment for one reason or another.

Third, the study population is not directly comparable to the general US population because the clinical trial was multinational and only 26.8% of patients were from the Americas. Additionally, patients enrolled in a clinical trial may experience different HRQoL than the general population.

Fourth, certain patients from earlier eltrombopag studies did not have a treatment-free interval to reset their baseline. Therefore, lack of greater improvement may have resulted from elevation of baseline platelet count and HRQoL by previously taken eltrombopag; however this would mean our current results would be conservative, as greater improvement would be expected if baseline were reset. This was addressed with sensitivity analysis assessing patients with baseline platelet counts of <30 × 10^9/L, which confirmed the robustness of results.

Lastly, HRQoL was not assessed after eltrombopag discontinuation.

6 | CONCLUSION

This study identified increases in HRQoL in patients with ITP during long-term eltrombopag treatment. It found positive associations between all HRQoL measures and platelet response using multiple definitions of response, especially with SF-36v2 PCS, FACIT-Fatigue, and FACT-Th6. Benefits from long-term eltrombopag therapy in increasing platelet counts often carried forward into alleviating fatigue, concerns about bleeding and bruising, and improvement in physical function. While not all patients, not even all responders, have substantial benefit in HRQoL, many individuals had substantial continuing improvements in HRQoL manifest in several instruments. The mechanism of this improvement remains to be clarified in future studies.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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