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Validation of Pain and Patient Global Scales in Chronic Gout: Data from Two Randomized Controlled Trials

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Abstract

Objective—To assess validity of pain and patient global scales in gout.

Methods—We used data from pegloticase clinical trials in chronic refractory gout to examine the validity of Visual analog scale (VAS) pain (0–100; 100=worst pain), Short-Form 36[®] (SF-36[®]) bodily pain (0–100; 100=no pain) and VAS patient global assessment (0–100; 100= worst score). Convergent/divergent validity was tested by examining their correlation with tender and swollen joints, disease duration, gout flares, comorbidities, plasma urate, health assessment questionnaire (HAQ) and SF-36[®] physical and mental component summary scores. For discriminant ability, we compared the change at 6 months between placebo and pegloticase arms and calculated effect size and standardized response mean (SRM).

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Results—212 patients (mean age, 55.4 years, 82% men; 73% with tophaceous gout) provided data. VAS pain was statistically significantly correlated with baseline tender and swollen joints, SF-36[®] summary and HAQ scores (all p-values <0.0001), but not disease duration (p=0.84), gout flares (p=0.08), comorbidities (p=0.47) or plasma urate (p=0.89). Same correlations were noted for patient global assessment (p<0.006 for all) and similar for SF-36 pain (p<0.002 for all). Pegloticase group had significantly more improvement than placebo at 6-months: VAS pain, -9.2(29.3) vs. 1.9(26.4), p=0.0002; SF-36[®] pain, 14.6(25.6) vs. -0.04(21.1), p<0.0001; and patient global, -9.3(26.5) vs. 3.4(22.8), p<0.0001. Effect size in pegloticase and placebo groups were as follows: VAS pain, 0.34 and -0.06; SF-36 pain, 0.69 and 0.00; patient global, 0.49 and -0.09.

Conclusion—VAS pain, SF-36 pain and patient global VAS are validated outcome measures in patients with chronic gout.

Keywords

Validation; Pain; Patient global; Gout; Discrimination; Omeract filter

INTRODUCTION

Gout is the most common inflammatory arthritis in men, characterized by episodes of acute inflammatory arthritis, which are associated with pain and inflammation. If untreated, patients develop chronic inflammatory arthritis characterized by chronic pain and inflammation, leading in some patients to tophaceous deposits and radiographic destruction. While most physicians consider pain to be a cardinal feature of acute gout, chronic gout is also associated with chronic inflammation which leads to morning stiffness and pain. Validation studies of any pain scale in chronic gout have not been done.

At the Outcomes Measures in Rheumatology Clinical Trials (OMERACT)-8 meeting in 2006, an international research organization of methodologists, 7 core domains were identified to be essential in assessment of patients with chronic gout by a consensus Delphi methodology. These included pain, patient global, activity limitation, health-related quality of life (HRQoL), tophus burden, acute gout attack and serum urate levels [1–3]. Short Form 36 (SF-36), as a measure of HRQoL, met the OMERACT filter of truth (face, content, construct and content validity), discrimination (sensitivity to change, discrimination between treatments) and feasibility and was validated as HRQoL measure [4]. The objective of this study was to examine whether patient reported pain and global assessments of disease activity are valid outcome measures for use in randomized controlled trials (RCTs) of chronic gout.

METHODS

Data Source-Description of Studies

Data source was from two International multi-center, replicate randomized, double-blind, dose-comparison, placebo-controlled 6-month Phase 3 clinical trials in patients with treatment-refractory gout (namely GOUT1 and GOUT2, also referred to as C0405 and C0406, respectively). The only differences were trial location (GOUT1: Sites in the U.S. and Canada; GOUT2: Sites in the U.S. and Mexico). In both trials, patients were randomized to

receive pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks or placebo in a 2:2:1 fashion. Stratification was done by the presence or absence of tophi. At baseline, all subjects had urate levels above 8 mg/dL. The data was pooled since the design of the two trials was identical.

Following two weeks screening period, every subject received a 2-hour infusion every two weeks for a total of 24 weeks of trial duration. Patient-reported outcomes, including the pain scales and patient global assessment of disease activity were administered at baseline, weeks 13, 19 and 25 (week 25 visit will be referred to 6-month visit from here onwards). Details of these trials have been described previously [5]. For the sake of simplicity, we used baseline and end of study (6-month) assessments for this study, since the end of study time-point is most likely to show difference between treatment and placebo.

Instruments for Validation

Pain and global assessment of disease activity were assessed by a single question each using a 100mm Visual analog scale (VAS). The pain item was- “How much pain have you had because of your illness in the past week?” The two anchors were “No pain” (score of 0) and “Severe pain” (score of 100). Patient global assessment question was: “Considering all the ways that your arthritis affects you, rate how you are doing today on the following scale by placing a vertical mark on the line”. The two anchors being “Very Well” (score of 0) and “Very Poor” (score of 100). In addition, we also examined the bodily pain domain of SF-36 version2 (SF-36v2®), a validated measure of HRQoL [6]. The SF-36 pain question was – “How much bodily pain have you had during the past 4 weeks? The responses (None, Very Mild, Mild, Moderate, Severe, Very Severe) are transformed to a 0–100 scale, with 100 being the best score (no pain) and 0 being the worst score (very severe pain). It is important to note that a score of 100 is the worst score for VAS pain and patient global VAS, but the best score for SF-36 pain scale.

Validation methods and statistical analyses

Truth—Truth for both pain measures and patient global assessment was assessed by face, content, construct and criterion validity. Face and content validity imply that a given instrument measures what it is supposed to measure (face) and whether it contains all the relevant content domains for the construct (content).

Convergent and divergent validity was assessed by Spearman correlation coefficients between each measure/instrument (pain VAS, SF-36 bodily pain and patient global VAS) and various other measures at baseline. We hypothesized that these instruments will have significant correlation with gout-related clinical characteristics (tender joints, swollen joints, disease duration and recent gout flares) and HRQoL and physical function likely impacted by gout ((SF-36®) and health assessment questionnaire (HAQ)). We also hypothesized that they will have low or no correlation with medical comorbidities and laboratory assessment of baseline plasma urate levels.

A Spearman’s correlation from 0.00 to 0.20 was interpreted as no correlation; 0.21–0.40 as low correlation; 0.41–0.60 as moderate correlation; 0.61–0.80 as marked correlation; and

0.81–1.00 as high correlation [7]. We also examined convergent/divergent validity by comparing the mean scores on pain and patient global VAS with SF-36® physical and mental component summary (PCS and MCS) quartiles, HAQ quartiles and categories of baseline swollen, baseline tender joints, baseline comorbidities (hypertension, renal failure, osteoarthritis, cardiovascular disease, diabetes, liver disorder, neoplasms), disease duration and plasma urate levels, using analysis of variance. Similar analyses for SF-36 bodily pain scores for baseline HAQ scores, swollen joints, tender joints, baseline comorbidity, disease duration and plasma urate (since PCS and MCS include SF-36 bodily pain domain in their calculations). We also tested for a linear trend, where significant associations were noted between baseline variables and each measure of interest. We hypothesized that patients with higher numbers of swollen, tender joints; more gout flares; and, longer gout duration will have worse pain and patient global scores, but not serum uric acid, comorbidities, and disease duration, as indicated by the strength of correlation. We also hypothesized that a linear trend would be observed between patient pain and global scores and worse SF-36® and HAQ scores and between patient global scores and medical comorbidities.

We examined the floor and ceiling effect by assessing the percent of VAS pain, SF-36 bodily pain and patient global ratings at maximal or minimal levels at baseline and end of study (6-month visit).

Discrimination—We compared the change scores in these measures between pegloticase treatment and placebo arms from baseline to end of study, to assess the discriminant ability of each measure. To assess responsiveness to change of the VAS pain, SF-36 bodily pain and patient global scales at 6 months, we estimated the Effect Size (ES) and Standardized Response Mean (SRM). ES was calculated by taking the change in mean pain scale from baseline to 6 months and dividing the result by the standard deviation at baseline. According to Cohen's rule, an ES of 0.20–0.49 represents a small change, 0.50–0.79 a medium change, and 0.80 a large change. SRM is defined as the mean change in the patient score with improvement divided by the SD of the changed scores. We calculated the Minimal Clinically Important Difference (MCID) [8], moderate CID and Really Important Difference (RID) for improvement in VAS and SF-36 pain as changes corresponding to 10 mm, 20 mm and 50 mm improvement on patient global assessment (anchor). A cut-off of 10 mm for defining MCID is consistent with a similar cut-off used in previous studies of 0–100 mm scales [9] [10] [11] [12] [13] [14] [15]. Moderate CID was considered with cut-off twice as much as MCID. The 50 mm cut-off for RID is similar to that defined previously, 3–4 times MCID [16].

Role of Funding Agency

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RESULTS

Description of study cohort

The study cohort characteristics are shown in Table 1. Characteristics are provided for each study separately and then for the two studies combined, as has been done previously for these two studies, which have been combined for analysis as per the FDA. Patients had a mean age of 55 years, 80% were men, and 67% were White. Mean number of tender joints was 12 and swollen joints, 10. 54% had gout disease duration of 5 years or more.

Truth

Face and Content Validity—VAS pain and SF-36 bodily pain domain ask patients about pain severity, and patient global assessment VAS scale asks patient about the global disease assessment; therefore, these measures have face and content validity. All three measures have been used extensively in several other conditions for decades and were used with febuxostat RCTs.

Convergent and Divergent validity—Baseline VAS pain had statistically significant moderate correlation with baseline tender joints, statistically significant low correlation with baseline swollen joints, but no significant correlation with disease duration or recent gout flares (Table 2). Moderate significant correlations with SF-36[®] PCS and HAQ scores, and low significant correlations with SF-36[®] MCS, were noted. As hypothesized, no significant correlation was noted with comorbidity score or plasma urate levels. Significantly higher VAS pain scores were noted in lower/worse SF-36[®] PCS and SF-36[®] MCS score quartiles ($p<0.0001$ for each) and with higher/worse HAQ quartiles ($p<0.001$), each with a significant linear trend ($p<0.01$) (Table 3; Appendix 1).

SF-36 bodily pain domain had significant and marked correlation with HAQ scores, significantly low correlations with baseline tender and swollen joints, but no correlation with disease duration or recent gout flares (Table 2). No significant correlations with comorbidity score or plasma urate levels were noted. Lower/better SF-36 bodily pain scores had significant association with lower numbers of tender and swollen joints and lower/better HAQ scores, each with statistically significant linear trends (Table 3; Appendix 2).

Patient global VAS scores had statistically significant low correlations with baseline tender joints and swollen joints, but no correlation with disease duration or recent gout flares (Table 2). Significant and moderate correlations with SF-36 PCS and MCS summary and HAQ scores were noted. No significant correlations/associations with baseline plasma urate levels or comorbidities were noted. Significantly higher SF-36 bodily pain scores were noted in patients with more swollen and tender joints ($p<0.001$ for each) and higher/worse HAQ score quartiles ($p<0.001$), with a significant linear trend noted for tender joints and HAQ scores ($p<0.01$), but not swollen joints (Table 3; Appendix 3).

As expected, statistically significant moderate to marked correlations were noted between these three outcomes measures: VAS pain, SF-36 bodily pain and patient global VAS.

Floor and Ceiling Effect—We noted minimal floor effects (<5%) for all three measures at baseline and slightly higher proportions for VAS pain (6%) and SF-36 bodily pain at the end of study (Table 4). Ceiling effects were almost absent for VAS pain (<2%) and patient global (<1%) scores at both baseline and at the end of the study: whereas, SF-36 bodily pain domain showed minimal ceiling effects at baseline (8%) and at end of study (<5%).

Discrimination

Discrimination between treatment arms—Decreases in VAS pain scores after 6-months of treatment with placebo were significantly less than those with either regimen of pegloticase 8 mg/kg (every 2 weeks or every 4 weeks; $p<0.0001$ for both), or both regimens combined ($p=0.0002$) (Table 5). Similarly, improvements in SF-36 bodily pain scores were significantly higher in each and combined pegloticase arms compared with placebo (Table 5; $p<0.0001$). Improvement in patient global assessment VAS was significantly better in pegloticase groups than placebo (Table 5; $p<0.0001$). For all three measures, changes with placebo at 6 months were in the direction opposite to that in the active treatment arms.

Clinically important change for improvement in Pain—MCID, moderate CID and RID for improvements in 0–100 mm VAS pain were 22.2, 29.6 and 50.2 units reduction, respectively (Table 5). MCID, moderate CID and RID for improvements 0–100 mm SF-36 bodily pain were 25.8, 29.9 and 41.7 unit change on 0–100 SF-36 pain scale (Table 5).

Sensitivity to change: Responsiveness statistics—The effect size for VAS pain, SF-36 bodily pain and patient global VAS scales were 0.34, 0.69 and 0.49, respectively, in the pegloticase arms (Table 6). Respective standardized response means were 0.30, 0.57 and 0.44 (Table 6).

Feasibility

VAS pain, SF-36 bodily pain and patient global assessment VAS are all single items; although not explicitly recorded, it takes less than 1 minute to complete these single items.

DISCUSSION

This is the first report to provide data regarding truth, discrimination and feasibility of two pain measures and a patient global measure in patients with chronic, tophaceous gout. Importantly, the data for this report was obtained from patients with chronic group enrolled in two replicate randomized, double-blind, dose-comparison, placebo-controlled Phase 3 clinical trials. All three measures analyzed from these trials, namely VAS pain, SF-36 bodily pain and patient global VAS scores, met the OMERACT filter of truth, discrimination and feasibility. These findings have particular relevance to RCTs in patients with chronic gout, since pain is a prominent feature of chronic gout. It is important to note that SF-36[®] instrument met the OMERACT filter as a HRQoL measure in gout [17–18] and has been endorsed by OMERACT [4]. In this study, we assessed whether SF-36 bodily pain question was a valid measure of pain in patients with chronic gout, in addition to examining VAS pain and patient global scales. Several findings deserve further discussion.

The measures being examined (pain VAS, SF-36 bodily pain and patient global VAS) correlated significantly with clinical characteristics, such as swollen and tender joints. Moderate to marked correlations with SF-36® and HAQ scores was not unexpected, given that patients in this study had chronic tophaceous gout, a condition associated with significant deficits in health related quality of life [17–18]. As expected, no significant correlations were noted with disease duration or plasma urate levels. These observations provide evidence for construct validity of VAS pain, SF-36 bodily pain and patient global assessments of disease activity. All three measures have been used extensively either as primary/secondary measures in RCTs in other rheumatologic conditions [19] or as part of composite measures in patients with other types of arthritis [20] [21].

Discriminant ability is one of the most important aspects of validation of an outcome measure for use in RCTs, if not the most important aspect. All three measures had discriminant ability, with significantly greater improvements observed for each measure in pegloticase arms compared with placebo. Based on these data, we propose that these validated measures can be used as patient-reported outcomes in clinical trials of chronic gout. The effect sizes of each of the three measures were moderate, ranging from 0.34 to 0.69, confirming that these measures are reasonable outcome measures for gout RCTs. Although we provide MCID estimates, we recognize that we used the cut-offs on patient global scales as anchors, which are not as desirable as using the changes corresponding to categorical response of “somewhat improved” or “much improved”. However, our estimates of 22–30 mm change (MCID and moderate CID) for clinically important improvement in pain are similar to 20 mm or 30% change suggested by Farrar et al. as clinically important in their meta-analyses of 10 RCTs of chronic pain [19] [22]. Two International groups, the Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [23] [24] and the International Association of Study of Pain (IASP) [25] have endorsed 30% and 50% improvement in pain (corresponding to moderately and substantially improved) to be reported in all clinical trials of pain. We agree that that the cut-offs of 30% and 50% improvements in these pain scales should be reported in chronic gout RCTs as well. The “really important difference (RID)” corresponded to 42–50 mm change in pain scales, which is similar to the substantial improvement of 50% in pain and is similar to ACR50 response in patients with rheumatoid arthritis [20].

Our study has several strengths and limitations. We examined data from two RCTs of pegloticase, a recently FDA-approved biologic therapy for adult patients with chronic gout refractory to conventional therapy. We presented data regarding convergent/divergent validity, responsiveness to change, floor/ceiling effect and estimates of clinically important improvements/differences. Estimates for clinically important differences ranged from 20–30 points, similar to estimates reported previously for these scales in other conditions. Several limitations must also be discussed. These data are derived from patients with chronic gout (71% with tophaceous gout), and whether these estimates will hold for cohorts with less severe disease and a smaller proportion with tophaceous gout remains to be seen. Male predominance may limit generalizability of study findings to women with gout. However, gout is a disease of middle-aged and older men; therefore, we anticipate these findings will be generalizable to most clinical trial cohorts. Reliability could not be tested in absence of test-retest or inter-rater assessments.

In conclusion, we have provided data for validation of two pain measures and patient global assessment in patients with chronic gout. Based on these data, VAS pain, SF-36 bodily pain and patient global VAS met the OMERACT filter of truth, discrimination and feasibility. Most randomized trials of patients with gout use instruments such as SF-36® and measures of pain; therefore, these instruments/measures are practical. The provision of clinically important difference allows future clinical trialists to power their clinical trials for these outcome measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KRYSTEXXA™ (pegloticase) is a PEGylated uricase enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Savient has exclusively licensed worldwide rights to the technology related to KRYSTEXXA and its uses from Duke University ("Duke") and Mountain View Pharmaceuticals, Inc. ("MVP"). Duke developed the recombinant uricase enzyme and MVP developed the PEGylation technology used in the manufacture of KRYSTEXXA™.

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Table 1

Demographic and clinical characteristics of trial population by each trial individually and data from both trial pooled

Characteristic	GOUT1 (Trial C0405) (n=104)	GOUT2 (Trial C0406) (n=108)	Pooled Data (n=212)
Age in years, Mean (SD)	56.8 (14.1)	54.0 (13.9)	55.4 (14.0)
Male, n (%)	80 (76.9)	93 (86.1)	173 (81.6)
Race/Ethnicity, n (%)			
White	78 (75.0)	65 (60.2)	143 (67.4)
American Indian or Alaskan Native	4 (3.8)	2 (1.8)	6 (2.8)
Asian	1 (1.0)	2 (1.8)	3 (1.4)
Black or African American	13 (12.5)	14 (13.0)	27 (12.7)
Hispanic or Latino	6 (5.8)	18 (16.7)	24 (11.3)
Native Hawaiian or Pacific Islander	0	5 (4.6)	5 (2.4)
Other	2 (1.9)	2 (1.8)	4 (1.9)
Number of tender joints, Mean (SD)	12.8 (13.3)	11.1 (13.8)	11.9 (13.5)
Number of swollen joints Mean (SD)	10.9 (11.4)	9.6 (11.3)	10.2 (11.3)
Duration of disease			
<1 year (%)	2 (1.9)	1 (0.9)	3 (1.4)
1–2 years (%)	5 (4.8)	6 (5.6)	11 (5.2)
2–5 years (%)	16 (15.4)	16 (14.8)	32 (15.1)
5–10 years (%)	22 (21.2)	18 (16.7)	40 (18.9)
>10 years (%)	59 (56.7)	67 (62.0)	126 (59.4)
Plasma urate level in mg/dl, Mean (SD)	9.7 (2.9)	9.6 (3.2)	9.7 (3.0)
Creatinine level, in mg/dl, Mean (SD)	1.5 (0.6)	1.4 (0.7)	1.5 (0.6)
Gout attacks/year in last year, Mean (SD)	7.6 (10.0)	5.6 (5.6)	6.5 (8.1)
Number of patients with tophi, n (%)	74 (71.2)	81 (75.0)	155 (73.1)
Patients with comorbidities, n (%)			
Hypertension	89 (85.6)	93 (86.1)	182 (85.8)
Renal failure (Creatinine $\geq$ 2 mg/dl)	45 (43.3)	27 (25)	72 (34.0)
Osteoarthritis	52 (50.0)	35 (32.4)	87 (41.0)
Cardiovascular disease	39 (37.5)	31 (28.7)	70 (33.0)
Diabetes	31 (29.8)	26 (24.1)	57 (26.9)
Liver disorders	3 (2.9)	8 (7.4)	11 (5.2)
Neoplasms	6 (5.8)	10 (9.3)	16 (7.5)

Table 2

Convergent and Divergent Validity measured with Spearman's correlation coefficients between patient characteristics at baseline and VAS Pain, SF-36pain and Patient-global

	VAS Pain N=211	SF-36 Pain N=211	Patient Global VAS N=191
Baseline Gout Clinical Characteristics			
Number of tender joints	0.42140 p<.0001	-0.27836 p<.0001	0.34851 p<.0001
Number of swollen joints	0.30317 p<.0001	-0.19152 0.0055	0.23498 0.0011
Disease duration in years	-0.01435 p=0.8358	-0.02073 p=0.7646	0.05492 p=0.4505
Number of gout flares/month in last year	0.11968 p= 0.0843	-0.11570 p= 0.0953	0.11635 p= 0.1099
Quality of life and functional limitation measures			
SF-36 Physical Component Summary (PCS)	-0.56353 p<.0001	N/A	-0.50241 p<.0001
SF-36 Mental Component Summary (MCS)	-0.36621 p<.0001	N/A	-0.41276 p<.0001
Health Assessment Questionnaire (HAQ) score	0.53848 p<.0001	-0.55851 p<.0001	0.50565 p<.0001
Comorbidity and Laboratory measures			
Comorbidity score (as in the table below)	0.05 p=0.47	-0.005 p=0.9425	0.08264 p=0.2557
Baseline Plasma Urate (mg/dl)	-0.00930 p= 0.8940	-0.00743 p= 0.9151	-0.05314 p= 0.4677

Significant p-values and correlations are in the **bold type**

N/A, not applicable, since SF-36 pain is a component of both PCS and MCS scales

Table 3

Convergent and Divergent validity: mean (SD) of selected patient characteristics and their association with VAS pain, HAQ pain and patient global VAS, with p-values with analysis of variance and p-value for linear trend.

	VAS Pain (0–100; 100=worst) N=211	SF-36 Pain (0–100; 100=best) N=211	Patient Global VAS (0–100; 100=worst) N=191
GOUT CLINICAL CHARACTERISTICS			
Baseline number of tender joints	p<0.0001 Linear trend, p<0.0001	p=0.009 Linear trend, p<0.0001	p<0.0001 Linear trend, p<0.0001
None (n=24) ^a	28.7 (22.0)	46.6 (20.9)	33.5 (25.3)
1–2 (n= 25)	36.6 (31.1)	44.0 (25.0)	40.9 (22.0)
3–5 (n=22)	32.9 (23.8)	41.8 (23.6)	36.9 (20.7)
5–10 (n=41)	48.9 (25.7)	35.3 (18.2)	49.0 (22.9)
>10 (n=80)	59.8 (24.5)	31.7 (20.8)	57.8 (24.4)
Baseline number of swollen joints	p<0.0001 Linear trend, p=0.076	p=0.01 Linear trend, p=0.048	p=0.005 Linear trend, p=0.51
Zero (n= 26)	30.9 (22.2)	45.7 (17.5)	37.5 (22.5)
1–2 (n= 25)	31.7 (29.5)	46.6 (28.8)	37.6 (23.5)
3–5 (n= 17)	35.0 (22.5)	45.2 (16.5)	36.4 (23.2)
5–10 (n= 57)	52.8 (24.5)	32.7 (19.6)	48.6 (25.4)
>10 (n= 69)	54.5 (28.3)	35.3 (24.1)	54.5 (24.7)
Baseline Disease duration	p=0.99 Linear trend, p=0.85	p=0.99 Linear trend, p=0.72	p=0.92 Linear trend, p=0.89
<1 year (n=0)	--	--	--
1–2 years (n=14)	48.3 (25.8)	38.1 (17.1)	44.5 (25.5)
>2–5 years (n= 31)	45.8 (26.1)	37.2 (20.4)	45.7 (25.2)
5–10 years (n=40)	46.3 (27.3)	38.3 (22.1)	49.2 (24.4)
>10 years (n=126)	46.6 (28.6)	37.4 (23.8)	47.5 (25.4)
Gout flares/month in the last year	p=0.95 Linear trend, p=0.58	p=0.08 Linear trend, p=0.03	p=0.57 Linear trend, p=0.90
0 (n=10)	53.1 (22.5)	40.3 (13.7)	55.4 (21.9)
>0–2 (n=34)	37.8 (29.1)	47.4 (22.7)	43.4 (27.6)
>2–6 (n=92)	45.4 (28.6)	38.0 (22.7)	44.1 (25.2)
>6–12 (n=49)	52.0 (23.6)	31.9 (20.6)	52.8 (20.6)
>12 (n=24)	49.5 (29.4)	32.0 (23.4)	51.2 (28.8)
QUALITY OF LIFE AND FUNCTIONAL ABILITY CHARACTERISTICS			
Baseline SF-36 PCS quartiles	p<0.0001 Linear trend, p<0.0001	N/A	p<0.0001 Linear trend, p<0.0001
Lowest quartile (n=52)	64.0 (19.7)	N/A	62.5 (22.3)
Second Lowest quartile (n=53)	55.4 (22.5)	N/A	51.0 (17.1)
Second Highest quartile (n=52)	43.7 (27.0)	N/A	49.8 (23.7)
Highest quartile (n=53)	22.6 (21.9)	N/A	25.2 (20.2)

	VAS Pain (0–100; 100=worst) N=211	SF-36 Pain (0–100; 100=best) N=211	Patient Global VAS (0–100; 100=worst) N=191
Baseline SF-36 MCS quartiles	p<0.0001 Linear trend, p=0.003	N/A	p<0.0001 Linear trend, p=0.0001
Lowest quartile (n=53)	62.9 (26.6)	N/A	65.1 (23.9)
Second Lowest quartile (n=52)	46.6 (23.2)	N/A	50.3 (21.1)
Second Highest quartile (n=53)	40.6 (26.5)	N/A	37.7 (22.8)
Highest quartile (n=52)	35.1 (26.4)	N/A	38.8 (23.0)
Baseline HAQ quartiles	p<0.0001 Linear trend, p=0.89	p<0.0001 Linear trend, p=0.44	p<0.0001 Linear trend, p=0.68
Lowest quartile (n=49)	23.8 (24.0)	57.0 (21.9)	27.6 (21.8)
Second Lowest quartile (n=54)	42.2 (25.4)	39.5 (20.0)	47.1 (20.8)
Second Highest quartile (n=46)	53.6 (24.3)	32.2 (19.2)	50.9 (23.7)
Highest quartile (n=61)	63.0 (20.8)	24.2 (15.4)	61.5 (21.1)
COMORBIDITY AND LABORATORY CHARACTERISTICS			
Baseline Comorbidity (sum of 7 comorbidities as listed in table 1^b)	p=0.72 Linear trend, p=0.68	p=0.90 Linear trend, p=0.87	p=0.61 Linear trend, p=0.97
Zero (n=31)	46.8 (28.9)	35.9 (21.2)	43.6 (26.7)
One (n=55)	42.9 (27.4)	38.8 (22.6)	44.5 (24.8)
Two (n=54)	47.6 (28.9)	38.6 (25.7)	49.6 (26.2)
Three or more (n=71)	48.4 (26.6)	36.6 (20.6)	48.9 (24.0)
Baseline Plasma Urate	p=0.54 Linear trend, p=0.88	p=0.50 Linear trend, p=0.34	p=0.54 Linear trend, p=0.50
<9.0 (n=75)	46.8 (26.9)	38.0 (19.7)	50.9 (23.3)
9 – <10 (n=43)	44.5 (27.0)	39.5 (24.7)	43.4 (24.0)
10 – <11 (n= 28)	53.8 (29.7)	31.3 (26.1)	48.3 (26.2)
11 – <12 (n=26)	41.2 (30.5)	41.7 (21.5)	43.1 (28.1)
12 (n=36)	46.2 (26.0)	37.9 (22.8)	46.7 (27.8)

N/A, not applicable

^a Number of patients with VAS pain or SF-36 pain with some patients missing values for tender/swollen joints and similar variables (numbers add up to 211 or less); Number of patients with patient global was slightly lower, as indicated by the lower number who provided this measure compared to VAS pain or SF-36 Pain

^b Sum of 7 comorbidities: osteoarthritis, hypertension, heart disease, diabetes, renal failure, neoplasms, liver disease

Table 4

Floor and Ceiling effect

	VAS Pain (0–100; 100=worst)	SF-36 Pain (0–100; 100=best)	Patient Global (0–100; 100=worst)
% at floor (score of 0 for VAS Pain and patient global; score of 100 for SF36 pain)			
Baseline, n/N (%)	9/211 (4.3)	3/211 (1.4)	5/191 (2.6)
Final, n/N (%)	13/210 (6.2)	17/212 (8.0)	7/190 (3.7)
% at ceiling (score of 100 for VAS Pain and patient global; score of 0 for SF36 pain)			
Baseline, n/N (%)	3/211 (1.4)	17/211 (8.1)	1/191 (0.5)
Final, n/N (%)	0/210 (0.0)	10/212 (4.8)	0/190 (0.0)

For VAS pain, N=211 at baseline and 210 at final visit; For SF-36, N^b=211 at baseline and 212 at final visit; For patient global, N^c=191 at baseline and 190 at final visit

Table 5
Discriminant Ability: Sensitivity to change from baseline to 6-months in each treatment arm

(values presented are mean change (standard deviation of the change)) and Estimates representing clinically important differences (CID)

	Change in VAS Pain (0–100; 100=worst) ^a	Change in SF36 Pain (0–100; 100=best) ^b	Change in Patient Global (0–100; 100=worst) ^a
Change = 6-month - Baseline value			
Placebo	1.9 (26.4)	–0.04 (21.1)	3.4 (22.8)
Pegloticase 8 mg every 4 weeks	–6.3 (27.8)	13.5 (24.5)	–9.7 (27.0)
Pegloticase 8mg every 2 weeks	–12.3 (30.4)	15.8 (26.7)	–8.9 (26.1)
<i>p-value (ANOVA) overall and post-hoc between three groups</i>	p<0.0001	p<0.0001	p<0.0001
Both Pegloticase groups pooled	–9.2 (29.3)	14.6 (25.6)	–9.3 (26.5)
<i>p-value comparing placebo to both pegloticase groups pooled</i>	0.0002	p<0.0001	p<0.0001
Clinically Important Improvement (baseline-6 month)			
10 mm reduction (MCID) (n=81)	–22.2 (29.3)	25.8 (23.8)	N/A
20 mm reduction (Moderate CID) (n=60)	–29.6 (26.7)	29.9 (24.6)	N/A
50 mm reduction (RID) (n=13)	–50.2 (22.9)	41.7 (23.9)	N/A

^a Negative number indicates improvement;

^b positive number indicates improvement;

^c Both overall and all post-hoc comparisons were statistically significant each with a p-value of <0.0001;

N/A, not applicable; MCID, minimal clinically important difference; CID, clinically important difference; RID, really important difference

Table 6

Responsiveness statistics for VAS pain, SF-36 pain and patient global VAS

	VAS pain (N=197)	SF-36 pain (N=199)	Patient global (N=178)
Effect Size (ES)			
Pegloticase both groups pooled	0.34 (n=156)	0.69 (n=156)	0.49 (n=139)
Placebo	−0.06 (n=41)	0.001 (n=43)	−0.09 (n=39)
Placebo and both pegloticase groups pooled	0.25 (n=197)	0.54 (n=199)	0.36 (n=178)
Standardized response mean (SRM)			
Pegloticase both groups pooled	0.30 (n=156)	0.57(n=156)	0.44 (n=139)
Placebo	−0.06 (n=41)	0.001 (n=43)	−0.09 (n=39)
Placebo and both pegloticase groups pooled	0.22 (n=197)	0.45 (n=199)	0.33 (n=178)

Effect size (ES) defined as the mean change score divided by the SD of baseline scores; standardized response mean (SRM) defined as the mean change score divided by the SD of changed scores;

^a Numbers were same for VAS and SF-36 pain for each arm; numbers were slightly lower for patient global, with 139 patients in pegloticase arms, 39 patients in placebo arm and 178 total patients contributing the data.