Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment
Two Randomized Controlled Trials

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Context Patients with chronic disabling gout refractory to conventional urate-lowering therapy need timely treatment to control disease manifestations related to tissue urate crystal deposition. Pegloticase, monomethoxy(polyethylene glycol)–conjugated mammalian recombinant uricase, was developed to fulfill this need.

Objective To assess the efficacy and tolerability of pegloticase in managing refractory chronic gout.

Design, Setting, and Patients Two replicate, randomized, double-blind, placebo-controlled trials (C0405 and C0406) were conducted between June 2006 and October 2007 at 56 rheumatology practices in the United States, Canada, and Mexico in patients with severe gout, allopurinol intolerance or refractoriness, and serum uric acid concentration of 8.0 mg/dL or greater. A total of 225 patients participated: 109 in trial C0405 and 116 in trial C0406.

Intervention Twelve biweekly intravenous infusions containing either pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase alternating with placebo at successive infusions (monthly treatment group), or placebo (placebo group).

Main Outcome Measure Primary end point was plasma uric acid levels of less than 6.0 mg/dL in months 3 and 6.

Results In trial C0405 the primary end point was reached in 20 of 43 patients in the biweekly group (47%; 95% CI, 31%-62%), 8 of 41 patients in the monthly group (20%; 95% CI, 9%-35%), and in 0 patients treated with placebo (0/20; 95% CI, 0%-17%; P<.001 and <.04 for comparisons between biweekly and monthly groups vs placebo, respectively). Among patients treated with pegloticase in trial C0406, 16 of 42 in the biweekly group (38%; 95% CI, 24%-54%) and 21 of 43 in the monthly group (49%; 95% CI, 33%-65%) achieved the primary end point; no placebo-treated patients reached the primary end point (0/23; 95% CI, 0%-15%; P=.001 and <.001, respectively). When data in the 2 trials were pooled, the primary end point was achieved in 36 of 85 patients in the biweekly group (42%; 95% CI, 32%-54%), 29 of 84 patients in the monthly group (35%; 95% CI, 24%-46%), and 0 of 43 patients in the placebo group (0%; 95% CI, 0%-8%; P<.001 for each comparison). Seven deaths (4 in patients receiving pegloticase and 3 in the placebo group) occurred between randomization and closure of the study database (February 15, 2008).

Conclusion Among patients with chronic gout, elevated serum uric acid level, and allopurinol intolerance or refractoriness, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower uric acid levels compared with placebo.

Trial Registration clinicaltrials.gov Identifier: NCT00325195

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progress to severe chronic gout characterized by frequent arthritic flares, chronic arthropathy, and enlarging tophi, often accompanied by deformity, chronic pain, functional disability, and impaired health-related quality of life (QOL). High rates of cardiovascular (CV), metabolic, and renal comorbidities further complicate QOL and management of individuals with chronic gout.

In contrast to nonprimate mammals, humans excrete UA rather than the soluble metabolite allantoin as the end product of purine metabolism because of mutational inactivation of the urate oxidase (uricase) gene. Pegloticase, a recently approved mammalian recombinant uricase conjugated to monomethoxypoly(ethylene glycol), is an enzymatic alternative to conventional urate-lowering agents. Intravenously administered (IV) pegloticase remains in the circulation where it rapidly degrades urate. We hypothesize that the resulting urate concentration gradient draws extravascular urate into the circulation for degradation and that persistent reduction of extracellular fluid urate concentration favors urate crystal dissolution, with eventual normalization of the body urate pool and resolution of gout symptoms and signs.

Single- and multiple-dose studies of pegloticase in patients with refractory gout have established dose-related UA reduction lasting several weeks after each IV infusion. In a 3-month randomized open-label efficacy and safety trial, profound and sustained urate lowering occurred most often when 8-mg pegloticase was infused every 2 weeks. Here, we report results of replicate, randomized, placebo-controlled, 6-month trials of the urate-lowering and clinical efficacy and tolerability of pegloticase in patients with refractory gout.

**METHODS**

Patients were 18 years or older and met the following criteria for refractory gout: a baseline serum UA of 8.0 mg/dL or greater (to convert to μmol/L, multiply by 59.485) and at least 1 of the following: 3 or more self-reported gout flares during the previous 18 months; 1 or more tophi; and gouty arthropathy, defined clinically or radiographically as joint damage due to gout. Patients also had contraindication to treatment with allopurinol or history of failure to normalize UA despite 3 or more monthly courses of treatment with the maximum medically appropriate allopurinol dose (determined by the treating physician). Exclusion criteria were glucose-6-phosphate dehydrogenase deficiency (because of hemolyosis/methemoglobinemia associated with administration of unmodified recombinant uricase), prior treatment with a uricase-containing agent, pregnancy, unstable angina, uncontrolled hypertension (>150/95 mm Hg) or cardiac arrhythmia, uncompensated congestive heart failure, renal dialysis, or solid organ transplant.

This study received institutional review board approval at each site. Written informed consent and Health Insurance Portability and Accountability Act assurances were completed for each participant before enrollment.

Two replicate, randomized, 6-month, double-blind, placebo-controlled trials (C0405 and C0406) were conducted at 56 rheumatology practices in the United States, Canada, and Mexico between June 2006 and October 2007. Starting at week 1, patients received 2-hour IV infusions of 250-mL 0.9% sodium chloride containing either pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase 8 mg alternating with placebo (every-4-week or monthly treatment group), or placebo (placebo group). As prespecified, the primary end point was analyzed separately for each trial, and safety and secondary end points were analyzed using data pooled from both trials. Randomization used an automated interactive voice response system and was stratified to ensure comparable numbers of patients with tophi in each group.

Participants receiving urate-lowering medication at screening underwent a 1-week washout. Gout flare prophylaxis (colchicine, 0.6 mg once or twice daily, or a nonsteroidal anti-inflammatory drug) was initiated 1 week before first infusion and continued throughout the study. Prophylaxis against infusion-related reactions (IRs) was given to all patients before each infusion: oral fexofenadine, 60 mg the evening before and again before infusion; acetaminophen, 1000 mg; and IV hydrocortisone, 200 mg, immediately before infusion.

**Efficacy End Points and Assessments**

The primary efficacy end point was the proportion of plasma UA responders in each pegloticase treatment group vs the placebo group. A responder was defined as a patient with plasma UA less than 6.0 mg/dL for 80% of the time or longer during both months 3 and 6, the periods extending, respectively, from the week-9 infusion to just prior to the week-13 infusion and from the week-21 infusion to the week-25 final study visit. Plasma UA (measured in trichloroacetic acid–precipitated chilled plasma) was chosen to study this end point in order to avoid possible ex vivo serum UA degradation by circulating pegloticase. Plasma UA was determined at baseline, at 2 and 24 hours after initial infusion, preceding each biweekly infusion, and at 5 additional prespecified time points in both month 3 and month 6: 2 hours, 1 day, and 7 days after the week-9 and week-21 infusions and 2 hours and 7 days after the week-11 and week-23 infusions.

Secondary end points included tophus resolution; reductions in the proportion of patients with gout flare and in the number of flares per patient during months 1-3 and 4-6 of the trial; reductions in tender joint count (TJC) and swollen joint count (SJC); and patient-reported changes in pain, physical function, and QOL, measured, respectively, by the Health Assessment Questionnaire (HAQ) pain scale, HAQ–Disability Index (HAQ-DI), and 36-Item Short Form Health Survey (SF-36).

Secondary end points were assessed at baseline, at the week-13 and week-19 visits, and at the week-25 final visit. For
tophus measurement, serial standardized digital photographs of hands and feet and up to 2 other sites with tophi were obtained and compared by a blinded central reader using computer-assisted quantitative measurement and key concepts of photographic assessment of skin tumors by Response Evaluation Criteria in Solid Tumors (RECIST) software (MedStudy version 4.4; Megasoft, Hyderabad, India). This validated method for evaluating quantitative response of malignant skin lesions to cancer treatments was applied based on analogy of tophaceous mass lesions to malignant skin lesions. A tophus complete response (CR) was defined as 100% reduction in the measured area of at least 1 tophus (of baseline diameter ≥5 mm) without growth of any baseline tophus or appearance of any new tophus.

Gout flare (acute joint pain and swelling requiring treatment) occurrence, duration, and severity were reported by patients at time of occurrence and confirmed by investigator interview. Each investigator assessed SJC and TJC in 54 specified joints. Patients completed HAQ and SF-36 forms. Values for SJC, TJC, and patient-reported end points were imputed using last observation carried forward for participants not completing all infusions and the week-25 final study visit.

Safety assessments included biweekly physical examination and medical history and adverse event (AE) updates and monthly complete blood counts, serum chemistry, and urinalysis. An AE occurring during infusion or within 2 hours after was declared an IR and prompted standardized assessment: physical examination, electrocardiogram, and measurement of serum tryptase (to detect significant mast cell degranulation).

All participant files were reviewed in a post hoc analysis by an independent, blinded CV event adjudication committee. Deaths and AEs considered possibly of CV type were assessed using the Anti-Platelet Trialists’ Collaboration (APTC) composite of end points for the primary analysis.

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CI, 9%-35%) and 49% (21/43; 95% CI, 33%-65%) in the 2 trials. Response rates were 0% in both placebo groups (95% CI, 0%-17% and 0%-15% in the 2 trials). Serum UA was also measured at most study time points, and the $\kappa$ coefficient, which provides a measure of agreement between corresponding se-

**Figure 1. Screening, Randomization, and Disposition During the Treatment Period for the Study Populations of Trial C0405 and Trial C0406**

**TRIAL C0405**

- 128 Patients assessed for eligibility
- 19 Excluded
  - 13 Exclusionary laboratory value
  - 3 Patients withdrew
  - 3 Other

- 109 Randomized
  - 44 Randomized to receive pegloticase every 2 weeks
  - 43 Randomized to receive pegloticase every 4 weeks
  - 41 Received ≥1 dose (mITT)
  - 2 Did not receive pegloticase

- 3-mo Assessment
  - 36 Assessed
  - 5 Withdrawn from trial

- 30 Completed study
  - 13 Total withdrawn from trial
  - 8 Adverse events
  - 3 Withdrew consent
  - 1 Protocol violation

- 37 Assessed
  - 6 Withdrawn from trial

- 23 Received ≥1 dose (mITT)
  - 20 Did not receive placebo

- 19 Completed study
  - 1 Total withdrawn from trial (lost to follow-up)

**TRIAL C0406**

- 134 Patients assessed for eligibility
- 18 Excluded
  - 15 Exclusionary laboratory value
  - 2 Patients withdrew
  - 1 Other

- 116 Randomized
  - 46 Randomized to receive pegloticase every 2 weeks
  - 42 Received ≥1 dose (mITT)
  - 4 Did not receive pegloticase

- 3-mo Assessment
  - 33 Assessed
  - 9 Withdrawn from trial

- 29 Completed study
  - 13 Total withdrawn from trial
  - 7 Adverse events
  - 1 Death
  - 5 Withdraw consent

- 32 Assessed
  - 6 Withdrawn from trial

- 23 Assessed
  - 5 Withdrawn from trial

The deaths occurred during the treatment period. Four additional patients died after randomization but outside of the treatment period: 1 patient randomized to the pegloticase biweekly treatment group and 3 patients randomized to the placebo treatment group. mITT indicates modified intent-to-treat group.
physical function and QOL compared with placebo. Patient-reported pain (visual analog scale) was significantly reduced (Table 2) with biweekly pegloticase vs placebo. Treatment with biweekly pegloticase was also associated with significant changes from baseline in HAQ-DI scores\textsuperscript{21} and SF-36 Physical Component Summary scores that met or exceeded the minimum clinically important differences established for the respective instrument in inflammatory arthritides (Table 2).\textsuperscript{12,34-37}

**Adverse Events**

One or more AEs occurred in more than 90% of participants in each treatment group (Table 3). Serious AEs occurred more frequently in patients treated with biweekly (24%; 95% CI, 15%-34%) and monthly pegloticase (23%; 95% CI, 14%-33%) than in patients receiving placebo (12%; 95% CI, 4%-25%). Gout flare was the most common AE and was reported in approximately 80% of patients across the 3 pooled study groups.

Infusion-related reaction was the second most common AE (occurring in 26%, 42%, and 5% of patients receiving pegloticase biweekly, pegloticase monthly, and placebo, respectively). Table 4 shows the specific AEs reported in at least 5% of patients across the 3 pooled study groups. The most frequent non-infection-related AEs were injection-site reactions and infusion-related reactions, occurring in more than 10% of patients in each treatment group. No deaths or cases of anaphylaxis were reported. No clinically meaningful differences in laboratory values were observed between treatment groups. No postmarketing cases of neoplasms were reported.

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**Table 1.** Baseline Characteristics for Trial C0405 and Trial C0406 (Modified Intent-to-Treat Group)

<table>
<thead>
<tr>
<th></th>
<th>Pegloticase Biweekly (n = 43)</th>
<th>Pegloticase Monthly (n = 41)</th>
<th>Placebo (n = 20)</th>
<th>Pegloticase Biweekly (n = 42)</th>
<th>Pegloticase Monthly (n = 43)</th>
<th>Placebo (n = 23)</th>
</tr>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.2 (15)</td>
<td>55.1 (13)</td>
<td>57.2 (13)</td>
<td>54.3 (16)</td>
<td>53.9 (14)</td>
<td>53.8 (11)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>30 (69.8)</td>
<td>35 (85.4)</td>
<td>15 (75.0)</td>
<td>38 (91.5)</td>
<td>34 (79.1)</td>
<td>21 (91.3)</td>
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<tr>
<td>White race/ethnicity, No. (%)\textsuperscript{a}</td>
<td>32 (74.4)</td>
<td>32 (78.0)</td>
<td>14 (70.0)</td>
<td>22 (52.4)</td>
<td>27 (62.8)</td>
<td>16 (69.6)</td>
</tr>
<tr>
<td>BMI, mean (SD)\textsuperscript{b}</td>
<td>34.85 (8)</td>
<td>33.68 (8)</td>
<td>33.30 (6)</td>
<td>31 (8)</td>
<td>32 (8)</td>
<td>31 (8)</td>
</tr>
<tr>
<td><strong>Gout characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration, mean (SD), y</td>
<td>16 (14)</td>
<td>16 (11)</td>
<td>12 (9)</td>
<td>15 (11)</td>
<td>16 (9)</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Acute flares in prior 18 mo, No. (quartiles)\textsuperscript{a}</td>
<td>43 (4, 8, 10)</td>
<td>40 (4, 7.5, 12)</td>
<td>20 (4.5, 8,12)</td>
<td>41 (4, 6, 10)</td>
<td>43 (4, 7, 10)</td>
<td>23 (3, 5, 10)</td>
</tr>
<tr>
<td>Baseline tophi, No. (%)</td>
<td>29 (67.4)</td>
<td>31 (75.6)</td>
<td>14 (70.0)</td>
<td>33 (78.6)</td>
<td>33 (78.7)</td>
<td>15 (65.2)</td>
</tr>
<tr>
<td>Chronic synovitis or arthropathy, No. (%)</td>
<td>27 (62.8)</td>
<td>23 (56.1)</td>
<td>13 (65.0)</td>
<td>23 (54.8)</td>
<td>24 (56.8)</td>
<td>13 (56.5)</td>
</tr>
<tr>
<td>Serum uric acid, mean (SD), mg/dL</td>
<td>9.8 (1.6)</td>
<td>10.4 (1.8)</td>
<td>9.4 (1.6)</td>
<td>9.5 (1.7)</td>
<td>9.6 (1.7)</td>
<td>9.8 (1.8)</td>
</tr>
<tr>
<td><strong>Comorbid conditions, No. (%)\textsuperscript{c}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (84)</td>
<td>36 (88)</td>
<td>17 (85)</td>
<td>36 (86)</td>
<td>35 (81)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>24 (56)</td>
<td>21 (51)</td>
<td>13 (65)</td>
<td>18 (43)</td>
<td>20 (47)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (30)</td>
<td>9 (20)</td>
<td>5 (25)</td>
<td>11 (28)</td>
<td>10 (23)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>10 (23)</td>
<td>5 (12)</td>
<td>6 (30)</td>
<td>10 (24)</td>
<td>4 (9)</td>
<td>1 (4)</td>
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<tr>
<td>Coronary artery disease</td>
<td>9 (21)</td>
<td>10 (24)</td>
<td>6 (30)</td>
<td>5 (12)</td>
<td>6 (14)</td>
<td>3 (13)</td>
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<tr>
<td>Cardiac failure/left ventricular dysfunction</td>
<td>8 (19)</td>
<td>4 (10)</td>
<td>4 (20)</td>
<td>4 (10)</td>
<td>4 (9)</td>
<td>2 (9)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>2 (10)</td>
<td>4 (10)</td>
<td>4 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td>0</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>29 (67)</td>
<td>27 (66)</td>
<td>14 (70)</td>
<td>21 (50)</td>
<td>28 (65)</td>
<td>10 (43)\textsuperscript{c}</td>
</tr>
<tr>
<td>Chronic kidney disease\textsuperscript{d}</td>
<td>12 (28)</td>
<td>13 (32)</td>
<td>6 (30)</td>
<td>14 (33)</td>
<td>12 (29)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>6 (14)</td>
<td>5 (12)</td>
<td>3 (15)</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Venous thromboembolic disease</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CV, cardiovascular.

\textsuperscript{a}Self-reported.

\textsuperscript{b}Calculated as weight in kilograms divided by height in meters squared.

\textsuperscript{c}Indicates 1 missing value.

\textsuperscript{d}Chronic kidney disease was defined as a creatinine clearance of less than 60 mL/min calculated with the Cockcroft-Gault equation.\textsuperscript{33}

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**Table 2.** End-Point Analyses for Primary and Secondary Outcomes (Pooled Modified Intent-to-Treat)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
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<tbody>
<tr>
<td><strong>Primary End Point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. responders/No. treated (%) [95% CI]\textsuperscript{b}</td>
<td>36/85 (42) [32 to 54]</td>
<td>29/84 (35) [24 to 48]</td>
<td>0/43 (0) [0 to 8]</td>
</tr>
<tr>
<td>P value\textsuperscript{c}</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>Trial C0405</td>
<td>20/43 (47) [31 to 62]</td>
<td>8/41 (20) [9 to 35]</td>
<td>0/20 (0) [0 to 17]</td>
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<tr>
<td>P value\textsuperscript{c}</td>
<td>&lt;.001</td>
<td>.04</td>
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<tr>
<td>Trial C0406</td>
<td>16/42 (38) [24 to 54]</td>
<td>21/43 (49) [33 to 65]</td>
<td>0/23 (0) [0 to 15]</td>
</tr>
<tr>
<td>P value\textsuperscript{c}</td>
<td>.001</td>
<td>&lt;.001</td>
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(continued)
### Table 2. End-Point Analyses for Primary and Secondary Outcomes (Pooled Modified Intent-to-Treat)\(^a\) (continued)

<table>
<thead>
<tr>
<th>Resolution of ≥1 tophi, No. patients/No. evaluable patients (%) [95% CI]</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months 1-4</td>
<td>21/52 (40) [27 to 55]</td>
<td>11/52 (21) [11 to 35]</td>
<td>2/27 (7) [1 to 24]</td>
</tr>
<tr>
<td>(P) value(^c)</td>
<td>.002</td>
<td>0.20</td>
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<table>
<thead>
<tr>
<th>Flare incidence, No. patients/No. treated (%) [95% CI]</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months 1-3</td>
<td>64/85 (75) [65 to 84]</td>
<td>68/84 (81) [71 to 89]</td>
<td>23/43 (53) [38 to 69]</td>
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<tr>
<td>(P) value(^c)</td>
<td>.02</td>
<td>0.02</td>
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<table>
<thead>
<tr>
<th>Flare frequency, No. flares per patient</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
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<tbody>
<tr>
<td>Months 1-3, mean (SD)</td>
<td>2.3 (2.1) (n = 85)</td>
<td>2.7 (2.4) (n = 84)</td>
<td>1.2 (1.6) (n = 43)</td>
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<tr>
<td>[95% CI] (quartiles)</td>
<td>[1.8 to 2.7] (1, 2, 4)</td>
<td>[2.2 to 3.2] (1, 2, 4)</td>
<td>[0.7 to 1.7] (0, 1, 2)</td>
</tr>
<tr>
<td>(P) value(^d)</td>
<td>.001</td>
<td>&lt;.001</td>
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<table>
<thead>
<tr>
<th>Tender joints, No. per patient</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
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<tr>
<td>Baseline mean (SD)</td>
<td>11.7 (13.0) (n = 84)</td>
<td>11.1 (13.5) (n = 83)</td>
<td>14.1 (14.8) (n = 43)</td>
</tr>
<tr>
<td>[95% CI] (quartiles)</td>
<td>[8.9 to 14.5] (1, 7, 18.5)</td>
<td>[8.1 to 14.0] (1, 4, 16)</td>
<td>[9.6 to 18.7] (3, 9, 21)</td>
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<tr>
<td>(P) value(^d)</td>
<td>.06</td>
<td>.45</td>
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<th>Swollen joints, No. per patient</th>
<th>Pegloticase Biweekly</th>
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<tbody>
<tr>
<td>Baseline, mean (SD)</td>
<td>8.9 (11.1) (n = 84)</td>
<td>10.1 (10.0) (n = 83)</td>
<td>13.2 (13.7) (n = 43)</td>
</tr>
<tr>
<td>[95% CI] (quartiles)</td>
<td>[6.5 to 11.3] (1, 5, 10)</td>
<td>[7.9 to 12.2] (2, 7, 15)</td>
<td>[8.9 to 17.4] (2, 11, 18)</td>
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<tr>
<td>(P) value(^d)</td>
<td>.08</td>
<td>.19</td>
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<th>HAQ-DI score(^e)</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean (SD)</td>
<td>1.10 (0.86) (n = 83)</td>
<td>1.21 (0.86) (n = 84)</td>
<td>1.24 (0.95) (n = 43)</td>
</tr>
<tr>
<td>[95% CI] (quartiles)</td>
<td>[0.92 to 1.29] (0.25, 1.00, 1.88)</td>
<td>[1.02 to 1.39] (0.38, 1.12, 2.00)</td>
<td>[0.94 to 1.53] (0.25, 1.12, 2.12)</td>
</tr>
<tr>
<td>(P) value(^d)</td>
<td>.43</td>
<td>.86</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HAQ pain score(^f)</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean (SD)</td>
<td>44.2 (27.7) (n = 84)</td>
<td>45.1 (27.0) (n = 84)</td>
<td>53.9 (28.1) (n = 43)</td>
</tr>
<tr>
<td>[95% CI] (quartiles)</td>
<td>[38.2 to 50.2] (21.5, 45.0, 68.0)</td>
<td>[39.2 to 50.9] (21.0, 50.0, 63.5)</td>
<td>[45.3 to 62.5] (29.3, 58.0, 75.0)</td>
</tr>
<tr>
<td>(P) value(^d)</td>
<td>.07</td>
<td>.09</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF-36 Physical Component Summary score(^g)</th>
<th>Pegloticase Biweekly</th>
<th>Pegloticase Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, mean (SD)</td>
<td>35.2 (10.9) (n = 83)</td>
<td>33.3 (9.8) (n = 84)</td>
<td>31.0 (11.1) (n = 43)</td>
</tr>
<tr>
<td>[95% CI] (quartiles)</td>
<td>[32.8 to 37.5] (27.1, 33.3, 43.1)</td>
<td>[31.1 to 35.4] (26.2, 33.1, 40.3)</td>
<td>[27.6 to 34.4] (22.0, 27.8, 39.3)</td>
</tr>
<tr>
<td>(P) value(^d)</td>
<td>.05</td>
<td>.26</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAQ, Health Assessment Questionnaire; HAQ-DI, HAQ–Disability Index; MCID, minimal clinically important difference; SF-36, 36-Item Short Form Health Survey.

\(^a\)Pooled data from the 2 replicate studies. As specified, the primary end point was analyzed separately for each study; key secondary end points were analyzed for the pooled population. Comparisons are between each treatment group and the corresponding individual or pooled placebo group. Numbers of patients for the analyses of tender joints, HAQ-DI, HAQ pain score, and SF-36 physical component summary score are for patients who had baseline and at least 1 follow-up assessment, with the final visit for each patient included (last observation carried forward).\(^28\)

\(^b\)Plasma uric acid values 6.0 mg/dL during 80% of the time during months 3 and 6.

\(^c\)Fisher exact test.

\(^d\)Two-sample \(t\) test (unequal variances).

\(^e\)Twenty questions regarding various physical activities including activities of daily living are scored from 0, “no difficulty,” to 3, “unable to do without help or use of aids.” The individual scores are averaged, with weighting for use of help, to obtain a final score between 0 and 10.\(^34\)-\(^36\)

\(^f\)Pain was scored from 0 to 100 mm on the HAQ visual analog scale.\(^12\),\(^36\),\(^37\)

\(^g\)SF-36 evaluates 12 domains spanning physical and mental components.\(^10\),\(^36\),\(^37\)
monthly, and placebo, respectively) and was also the most common reason for study discontinuation among pegloticase-treated patients (10% for biweekly; 13% for monthly). Serious IRs occurred in 5% (pegloticase biweekly) and 8% (pegloticase monthly) of patients. Resolution of all IRs began within minutes of slowing or discontinuing the infusion or initiating supportive treatment (which included epinephrine in 1 patient). All IRs resolved completely. Serum tryptase levels were increased in 12 of 108 IRs (10.2%), including 3 instances of IR classified as serious. In a retrospective analysis of IRs, 5 patients experienced IRs with signs and symptoms that met the criteria for anaphylaxis from the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network. These included 2 patients each in the pegloticase biweekly and pegloticase monthly cohort and a fifth patient who experienced these clinical features during the first infusion of the biweekly regimen. All of these reactions were judged as mild to moderate in severity by the investigator; 2 patients were treated with antihistamines and 1 with glucocorticoids. Serum tryptase activity was elevated in 1 of 5 patients. All signs and symptoms resolved completely in these 5 patients, and 3 of 5 continued in the trial.

Seven deaths (4 among patients assigned pegloticase and 3 in the placebo group) occurred between randomization and closure of the study database (February 15, 2008). One patient randomized to placebo died before the first infusion; 3 patients, each assigned pegloticase, died during the 6-month treatment period; and 3 patients (1 assigned pegloticase and 2 placebo) died after completing the treatment period (Figure 1 and Table 3). Two deaths during the treatment period were attributed to CV AEs (cardiac arrest in a 61-year-old man and arrhythmia in a 69-year-old man) in the biweekly pegloticase group. The third treatment period death resulted from renal failure in a 64-year-old man (monthly pegloticase) who withdrew from dialysis initiated during a hospitalization.

Three APTC events were identified by the adjudication committee: 2 CV non-CV related deaths occurring outside the treatment period included methicillin-resistant Staphylococcus aureus sepsis in an 89-year-old man 12 weeks after completing biweekly pegloticase treatment; recurrent chronic lymphocytic leukemia in an 80-year-old man receiving placebo; and multiorgan failure in an 85-year-old woman who was randomized to placebo but died before infusion. One death (cause indeterminate because of insufficient information) occurred 4 months after study withdrawal in a 67-year-old placebo-treated man with a history of congestive heart failure and insulin-dependent diabetes mellitus.

Responders are patients in each treatment group sustaining plasma uric acid (UA) levels of less than 6.0 mg/dL for 80% of the time in months 3 and 6 of the trial; nonresponders are patients in each group not sustaining UA levels less than 6.0 mg/dL throughout the trial. All patients treated with placebo were nonresponders. Plasma UA levels were determined at baseline; at 2 and 24 hours after the first infusion (which occurred at week 1); before each biweekly infusion; and at 2 hours, 1 day, and 7 days after the week-9 and week-21 infusions. Achievement or failure to achieve responder status was determined for each patient from a plot made from the multiple UA determinations during months 3 and 6. Dotted line indicates treatment response threshold; error bars indicate 95% confidence intervals.
TABLE 3. Number of Pooled Replicate Modified Intent-to-Treat Group Patients Experiencing Treatment-Emergent Adverse Events\textsuperscript{a}

<table>
<thead>
<tr>
<th>Event</th>
<th>Pegloticase Biweekly (n = 85)</th>
<th>Pegloticase Monthly (n = 84)</th>
<th>Placebo (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>80 (94)</td>
<td>84 (100)</td>
<td>41 (96)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>20 (24)</td>
<td>19 (23)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Death\textsuperscript{b}</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation owing to AE</td>
<td>15 (18)</td>
<td>16 (19)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gout flare</td>
<td>65 (76)</td>
<td>71 (85)</td>
<td>35 (81)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>22 (26)</td>
<td>35 (42)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (9)</td>
<td>9 (11)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (12)</td>
<td>6 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (4)</td>
<td>7 (8)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (7)</td>
<td>4 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5 (6)</td>
<td>4 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (4)</td>
<td>5 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Contusion</td>
<td>7 (8)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (2)</td>
<td>5 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>0</td>
<td>6 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Adjudicated CV events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTC events</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>CV death</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0</td>
<td>1 (1)\textsuperscript{c}</td>
<td>0</td>
</tr>
<tr>
<td>Non-APTC events</td>
<td>3 (2)\textsuperscript{d}</td>
<td>6 (7)</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>TIA</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; APTC, Anti-Platelet Trialists’ Collaboration; CHF, congestive heart failure; CV, cardiovascular; DVT, deep vein thrombosis; MI, myocardial infarction; TIA, transient ischemic attack.

\textsuperscript{a}A treatment-emergent AE was defined as any event (except death) reported with a start date occurring on or after the date of the first dose or any pre-existing condition that worsened on or after the first dose. Adverse events were categorized according to codes used in the Medical Dictionary for Regulatory Activities (MedDRA version 9.0) and listed in descending order of total AEs for each item.

\textsuperscript{b}Deaths recorded are those occurring during the 25-week treatment period. Additional deaths occurring in randomized patients outside the treatment period are described in the “Results” section.

\textsuperscript{c}The most commonly reported AEs were defined as those occurring in \( \geq 5\% \) of patients in any treatment group and at least 1% more frequently in patients treated with pegloticase compared with patients receiving placebo.

\textsuperscript{d}One patient had an APTC event (nonfatal myocardial infarction) and a non-APTC event (coronary revascularization), both recorded here.

\textsuperscript{e}One patient had 2 non-APTC events (CHF and arrhythmia) and is not counted twice in the total percentage of affected patients.

Deaths in patients treated with biweekly pegloticase (described in preceding paragraph) and 1 nonfatal myocardial infarction in a pegloticase monthly patient. All APTC events occurred in patients with 4 or more CV risk factors at baseline. Serious non-APTC events occurred in 2 patients in the biweekly group (2.3%; 95% CI, 0.3%-8.2%), 6 patients in the monthly group (7.1%; 95% CI, 2.7%-14.9%), and 0 patients in the placebo group (95% CI, 0%-8.2%). All non-APTC events occurred in patients with prior histories of CV disease but were not clustered by event category or duration of pegloticase treatment.

**Immunogenicity**

Antibodies to pegloticase appeared early in treatment and were detected in 134 of 150 patients treated with pegloticase (89%; 95% CI, 83%-94%). Pegloticase antibody was of IgM and IgG isotypes and, with the exception of antibody from 1 patient, did not neutralize pegloticase activity in vitro.

Only 1 of 52 (2%; 95% CI, 0.0%-10%) pegloticase-treated patients with pegloticase antibody exceeding a titer of 1:2430 at any time maintained a urate-lowering response to therapy. In contrast, 52 of 82 (63%; 95% CI, 52%-74%) pegloticase-treated patients who remained in the study for 2 months or longer and never had pegloticase-antibody titer greater than 1:2430 maintained their urate-lowering responses. A post hoc analysis comparing response rates in patients with and without antibody titers exceeding 1:2430 revealed a significant difference (\( P < .001 \)).

Antibody titers against pegloticase may also have been associated with the incidence of IRs in the 2 trials. Infusion-related reactions were reported in 31 of 52 patients (60%; 95% CI, 45%-72%) with pegloticase-antibody titers greater than 1:2430 at any time during the trial, compared with 16 of 84 patients (19%; 95% CI, 11%-29%) in whom pegloticase-antibody titer never exceeded 1:2430 (\( P < .001 \)). Although IRs were more common in patients with high titers of pegloticase antibody at some point during treatment, antibody titers at the time of occurrence of the first IR did not reliably predict IR. In contrast and importantly, a post hoc analysis found that loss of urate-lowering efficacy (plasma UA > 6.0 mg/dL) preceded the first IR in 91% (20/22 receiving biweekly pegloticase; 95% CI, 71%-99%) and 71% (24/34 receiving monthly pegloticase; 95% CI, 53%-85%) of patients with IRs.

**COMMENT**

These parallel, 6-month, placebo-controlled trials of pegloticase treatment have documented sustained UA reductions and significant clinical improvements in a substantial proportion of patients with chronic gout and refractoriness to, or intolerance of, conventional urate-lowering therapy.
significant disease-modifying benefits of pegloticase given every 2 weeks (to- 
phus resolution, reduced flare fre- 
quency, reduction in TJC, and im-
proved patient-reported outcomes in 
pain, physical function, and QOL) were 
demonstrable within 6 months, a time 
frame unique in randomized con-
trolled trials of urate-lowering agents.7,8 

As documented here and previously 
reported,11,12 chronic gout is associated 
with decreased physical function and 
diminished QOL. Improvements in physi-
cal function and QOL scores exceeding 
the minimal clinically important differ-
ence in pegloticase-treated patients, 
coupled with deterioration in pain and 
QOL in placebo-treated patients, pro-
vide evidence that chronic elevations in 
UA are associated with significant func-
tional impairment as measured by se-
veral criteria. This relationship has pre-
viously been difficult to distinguish from 
functional impairment imparted by se-
rious comorbidities that typically char-
acterize gout patients, and therefore, the 
ability of pegloticase to improve pa-
tient reported outcomes in this context is 
noteworthy.

Infusion-related reactions, includ-
ing some cases fulfilling criteria for ana-
phylaxis, were the most common AEs 
causing withdrawal from these trials. 
Although all IRs resolved promptly and 
without sequelae, minimizing the risk 
for IRs is important for the safe ad-
ministration of pegloticase in clinical 
practice.10 In our post hoc analysis, we 
observed the numerical im-
balance in these events underlines the 
need for care in selecting patients for 
pegloticase treatment. All patients who 
had serious CV events had baseline CV 
risk factors or previous events; thus, 
measures to stabilize CV comorbid-
ities prior to and during pegloticase 
treatment would be appropriate.

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Savient Pharmaceuticals, East Brunswick, New Jersey 
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Author Contributions: Dr Becker had full access to all 
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analysis.

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Statistical analysis: Huang, Maroli, Hamburger, Becker.

Obtained funding: Horowitz, Maroli.

Administrative, technical, or material support: Edwards, White, Horowitz, Maroli, Waltrip, Hamburger.

Study supervision: Horowitz, Maroli, Becker.

Conflict of Interest Disclosures: Dr Horowitz, Huang, 
Maroli, and Waltrip were employees of Savient Phar-
maceuticals at the time of conception and perfor-
mation of the reported study. Dr Sundy reported re-
serving fees for consulting and grant support from Savient 
Pharmaceuticals, Ardea Biosciences, Nuon Therapeu-
tics, Regeneron, and Novartis and payment for lec-
tures, including service on the speakers’ bureau, for 
Takeda Pharmaceuticals North America, Vicrpharma 
Duke University, Dr Sundy’s institution, may receive roy-
alties as a result of the licensing agreement with Savi-
ent Pharmaceuticals, an institutional conflict-of-
interest management plan is in place and Dr Sundy does 
not receive royalties or financial remuneration in 
relationship to this licensing agreement. Dr Baraf 
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meeting on pegloticase in June 2009; serving as a site 
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Novartis, URL/Mutual Pharmaceuticals, and Takeda 
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principal investigator for the current trial, for which a 
grant was provided to his institution; receiving travel 
expense reimbursement from Savient; and serving as 
investigator for a clinical trial sponsored by Savient 
Pharmaceuticals North America, for which a grant was 
paid to his institution. Dr Edwards reported consult-
ing income from Savient Pharmaceuticals, Takeda Phar-
maceuticals North America, Ardea Biosciences, Va-
ristis, and Regeneron. Dr Treadwell reported serving as 
a site principal investigator for the current trial, for which a 
grant was provided to his institution; receiving travel 
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consulting fees for services and/or meeting expenses for 
Ardea Biosciences, Nuon Therapeutics, Regeneron, 
Novartis,URL/Mutual Pharmaceuticals, and Takeda 
Pharmaceuticals. Dr Yood reported receiving consulting fees from Savient for participation in this study and/or preparation/attendance at the FDA Arthritis Advisory Committee meeting on pegloti-
case in June 2009. Dr Horowitz reported consulting for Ardea Biosciences in 2010 after leaving Savient Pharmaceuticals and holding stock and stock options in Savient at the time the study was performed and analyzed but having no financial interest in the com-
pany at the time of this submission. Dr Huang re-
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having no financial interest in the company at the time 
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ing stock and/or stock options in Savient. Drs 
Becker, Edwards, Gutierrez-Urena, Treadwell, 
and White reported receiving consulting fees from Savient 
for participation in this study and/or preparation/ 
attendance at the FDA Arthritis Advisory Committee 
meeting on pegloticase in June 2009; serving as a site 
principal investigator for the current trial, for which a 
grant was provided to his institution; receiving travel 
expense reimbursement from Savient; and receiving 
fees from Takeda Pharmaceuticals, BioCryst Pharma-
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Pharmaceuticals, and Regeneron for consultation re-
arding research and development of gout-related 
products; and receiving fees from UpToDate, where he 
editis the section on crystal-induced arthritis. No other authors reported conflicts.

Funding/Support: The work described in the manu-
script was funded by Savient Pharmaceuticals.

Role of the Sponsor: Savient Pharmaceuticals author-
ship employees were responsible for the study concept and 
design in consultation with the academic authors and 
with representatives of the US Food and Drug Admi-
nistration (FDA). Savient Pharmaceuticals, Kendle Inter-
national (a contract research organization), Charles River

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Laboratories, and ICON Laboratories (the central labo-
atory facility) were responsible for data acquisition 
and storage. The academic authors also participated in 
data acquisition as site (principal) investigators in the 
trials. Initial analysis of data was carried out by the 
sponsoring Therapeutics and immediately pre-
vented for critical review and interpretation to the par-
ticipating academic authors. Additional reviews of 
immunologic and cardiovascular data were carried out 
by the sponsoring Therapeutics and independently 
reviewed by specific experts in these areas. Drafting of the manuscript was undertaken by the 
academic and sponsor-employee authors, and all 
authors participated in critical manuscript revision for 
textual content. The academic authors deter-
mined the content of the final manuscript both before 
and after submission to the independent statistical 
reviewers. Representatives of the academic authors (DrS 
Becker and Sundy) participated in discussions with the 
independent statistical reviewers after the review to 
clarify issues of concern.

Independent Statistical Analysis: All efficacy and 
primary safety results and conclusions presented in this 
article have been confirmed by an independent sta-
tistical review performed by J. Wei, PhD, Department of Biostatistics, Harvard University. Dr. Wei was provided all raw SAS data sets, analysis SAS data 
sets, the study protocol containing a statistical analy-
sis plan, a blank copy of the study case report forms, 
and the original version of the manuscript by the au-
thors and sponsor of this study. Dr. Wei was in agree-
ment with the statistical methods used in the manu-
script and independently verified the primary and 
secondary efficacy and tolerability results; the results 
presented herein are those verified by Dr. Wei. Dr. Wei 
was compensated by Savient Pharmaceuticals for his 
independent statistical review.

Previous Presentation: Abstracts relating to this work 
were presented at the American College of Rheuma-
tology/Association of Rheumatology Health Profes-
sionals Annual Scientific Meetings; October 24-29, 
2008; San Francisco, California; and October 17-21, 
2009; Philadelphia, Pennsylvania; the European League 
Against Rheumatism Annual European Congress; June 
10–13, 2009, Copenhagen, Denmark; the American 
Society of Nephrology Annual Scientific Meeting; Oc-
tober 31-November 1, 2009; San Diego, California; 
the American Transplant Congress; May 30–June 3, 
2009; Boston, Massachusetts; the Infusion Nurses So-
ciety Annual Meeting; May 16–21, 2009; Nashville, 
Tennessee; the American Society of Clinical Pharma-
cology and Therapeutics Meeting; March 17–20, 2010; 
Atlanta, Georgia; and the American College of Rheu-
matology/Association of Rheumatology Health Pro-
fessionals Annual Scientific Meetings; November 7–11, 
2010, Atlanta.

Online-Only Material: The eMethods and 
efigures 1 and 2 are available at http://www.jama. 
com.

Additional Contributions: Savient Pharmaceuticals has 
licensed worldwide rights to the technology related to 
pegolitace from Duke University and Mountain 
View Pharmaceuticals. Members of the Cardiovascu-
lar Event Adjudication Committee were William B. 
White, MD (chair), Glen E. Cooke, MD, and Philip 
Gorelick, MD, who were compensated for their par-
ticipation.

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