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, monomethoxypoly(ethylene 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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LONG-TERM URATE-LOWERING therapy in gout aims to prevent or reverse tissue urate crystal deposits and associated symptoms and signs by maintaining concentrations of uric acid (UA) below the limit of solubility (6.8 mg/dL).[1,2] However, it is common for UA levels to exceed the recommended goal urate range of less than 6.0 mg/dL[2] during oral urate-lowering therapy among the 5 to 6 million US patients with gout,[3,4] a finding documented in a majority of individuals treated with the most frequently prescribed doses of allopurinol (≤300 mg/d).[5-8] Although dose titration of available oral urate-lowering agents can achieve target UA in most patients, urate-lowering therapy fails for perhaps 3% of patients[9] because of refractoriness, contraindication, or intolerance. Without effective urate lowering, many such patients

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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).[10-12] High rates of cardiovascular (CV),[13,14] metabolic, and renal comorbidities[15] 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.[16] Pegloticase, a recently approved[9] mammalian recombinant uricase conjugated to monomethoxypoly(ethylene glycol),[17-19] is an enzymatic alternative to conventional urate-lowering agents. Intravenously administered (IV) pegloticase remains in the circulation where it rapidly degrades urate.[17,18] 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[17,18,20] have established dose-related UA reduction lasting several weeks after each IV infusion. In a 3-month randomized open-label efficacy and safety trial,[20] 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 months of treatment with the maximum medically appropriate allopurinol dose (determined by the treating physician). Exclusion criteria were glucose-6-phosphate dehydrogenase deficiency (because of hemolysis/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,[21] HAQ–Disability Index (HAQ-DI),[22-24] and 36-Item Short Form Health Survey (SF-36).[25,26]

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 (MedStudio version 4.4; Megasoft, Hyderabad, India).[27] 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[28] 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.[29] Non-APTC serious CV events were identified from a modified list[30] of additional serious CV AEs.

Serum samples for pegloticase-antibody and pegloticase neutralization assays were obtained before infusions at weeks 1, 3, 5, 9, 13, 17, 21, and 25. Standard ELISA methodology was used to detect IgM, IgG, and total pegloticase antibody using pegloticase as capture antigen and horseradish peroxidase–conjugated secondary antibody.[31,32] (See eMethods for assay details, available at http://www.jama.com.)

Statistical Analyses

A modified intent-to-treat population (randomized patients who received at least 1 infusion) was used for all efficacy and safety determinations except for deaths, which were tracked for all patients from randomization to study database closure and recorded as occurring before, during, or after completion of the 25-week treatment period. Each replicate trial was considered adequately powered (>80%) to demonstrate a difference in responder rates of 35% vs 5% between each active treatment group and the respective placebo treatment group (significance level of $P = .05$ for each comparison).

Comparisons of baseline demographics and disease characteristics across treatment groups were made using analysis of variance for continuous parameters and the χ^2 test for categorical parameters. The primary efficacy of pegloticase in each trial was evaluated in responder analyses, with patients who withdrew before the week-25 final visit designated nonresponders. The proportion of responders in each pegloticase treatment group was compared with that in the corresponding placebo group using the Fisher exact test.

Numbers of patients with a tophus CR were compared between each pegloticase group and the placebo group using the Fisher exact test. Flare frequencies during months 1-3 and 4-6 were analyzed separately using the 2-sample *t* test, comparing each pegloticase group with placebo. Numbers of patients reporting flares during these periods were compared using the Fisher exact test. Comparisons of change from baseline for TJC and SJC and in pain scores, HAQ-DI scores, and SF-36 domains between each pegloticase group and the placebo group used the 2-sample *t*-test.

Two-sided analyses were performed for all statistical tests. *P* values less than .05 were considered significant. All statistical analyses were performed using Stata/SE version 11.2 (StataCorp, College Station, Texas).

RESULTS

A total of 225 participants (109 in trial C0405 and 116 in trial C0406) were randomized to the 3 study groups (pegloticase biweekly or monthly or placebo) in a 2:2:1 ratio (FIGURE 1). All urate-lowering, clinical efficacy, and tolerability analyses (except deaths) were carried out on a modified intent-to-treat population (n=212; 104 in trial C0405 and 108 in trial C0406) comprising all randomized patients who received at least 1 infusion. Baseline characteristics were similar across the trials and treatment groups; metabolic and renal disorders were common and CV comorbidities or risk factors were present in more than 80% of study participants (TABLE 1).

Primary Efficacy End Point

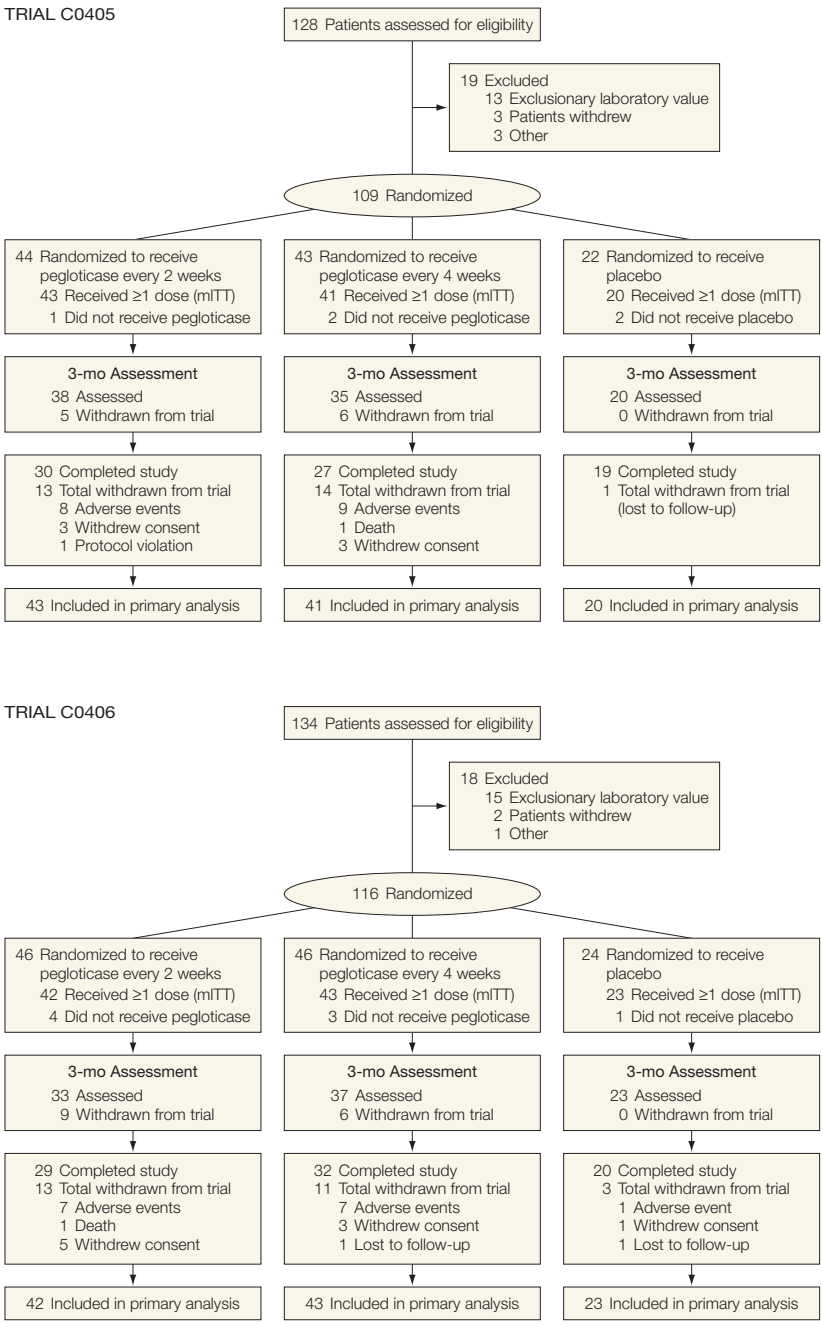
Plasma UA normalized within 24 hours of the first infusion in all patients receiving pegloticase, but afterward, some patients lost the urate-lowering response whereas others maintained UA less than 6.0 mg/dL throughout the trial. The proportion of UA responders (defined as a plasma UA <6.0 mg/dL for ≥80% of the time during months 3 and 6) in both pegloticase treatment groups was significantly greater than for the placebo group in the pooled analysis ($P < .001$ for both) (TABLE 2) and in the individual trials. When analyzed separately by dose, patients treated with biweekly pegloticase experienced response rates of 47% (20/43; 95% CI, 31%-62%) and 38% (16/42; 95% CI, 24%-54%) in the 2 trials. Patients treated with monthly pegloticase reported response rates of 20% (8/41; 95%

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 κ coefficient, which provides a measure of agreement between corresponding serum and plasma UA values, was 0.74 ($P<.001$), indicating near excellent agreement between the 2 methods.

Mean plasma UA for responders was substantially below 6.0 mg/dL for the entire 6-month treatment period (FIGURE 2). For nonresponders treated with biweekly pegloticase, mean plasma UA remained below 6.0 mg/dL through week 10 but was above target levels at all subsequent time points (Figure 2B). These findings suggest that a loss of urate-lowering efficacy manifested relatively early following treatment initiation. Among 74 patients treated with pegloticase (33 of 85 in the biweekly cohort and 41 of 84 in the monthly cohort) who lost urate-lowering efficacy prior to trial completion or withdrawal, 72 did so by month 4.

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



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.

Secondary End Points

Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a CR for 1 or more tophi by the final visit compared with 7% of patients receiving placebo ($P=.002$ and $P=.20$, respectively) (Table 2). Examples of tophus size reductions in patients receiving pegloticase therapy are shown in eFigure 1 and eFigure 2. During months 1-3, both the incidence of gout flares (proportion of patients suffering at least 1 flare) and the number of flares per patient were higher for pegloticase-treated patients compared with the placebo group (Table 2). However, with continued treatment during months 4-6, significant reductions were seen in the proportion of patients with gout flare in the biweekly treatment group vs the placebo group (Table 2). Flares per patient were also numerically fewer during this period with biweekly pegloticase treatment compared with placebo treatment, but the difference was not significant. There were also reductions in TJC and SJC in patients treated with pegloticase compared with the respective values in placebo recipients, but only differences in TJC were statistically significant (Table 2).

Both pegloticase dosing groups reported significant improvements in

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[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).[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

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

	Trial C0405			Trial C0406		
	Pegloticase Biweekly (n = 43)	Pegloticase Monthly (n = 41)	Placebo (n = 20)	Pegloticase Biweekly (n = 42)	Pegloticase Monthly (n = 43)	Placebo (n = 23)
Demographics						
Age, mean (SD), y	58.2 (15)	55.1 (13)	57.2 (13)	54.3 (16)	53.9 (14)	53.8 (11)
Male sex, No. (%)	30 (69.8)	35 (85.4)	15 (75.0)	38 (91.5)	34 (79.1)	21 (91.3)
White race/ethnicity, No. (%)[a]	32 (74.4)	32 (78.0)	14 (70.0)	22 (52.4)	27 (62.8)	16 (69.6)
BMI, mean (SD)[b]	34.85 (8)	33.68 (8)	33.30 (6)	31 (6)	32 (8)	31 (8)
Gout characteristics						
Duration, mean (SD), y	16 (14)	16 (11)	12 (9)	15 (11)	16 (9)	15 (10)
Acute flares in prior 18 mo, No. (quartiles)[a]	43 (4, 8, 10)	40 (4, 7.5, 12)	20 (4.5, 8,12)	41 (4, 6, 10)	43 (4, 7, 10)	23 (3, 5, 10)
Baseline tophi, No. (%)	29 (67.4)	31 (75.6)	14 (70.0)	33 (78.6)	33 (76.7)	15 (65.2)
Chronic synovitis or arthropathy, No. (%)	27 (62.8)	23 (56.1)	13 (65.0)	23 (54.8)	24 (55.8)	13 (56.5)
Serum uric acid, mean (SD), mg/dL	9.8 (1.6)	10.4 (1.8)	9.4 (1.6)	9.5 (1.7)	9.6 (1.7)	9.8 (1.6)
Comorbid conditions, No. (%)						
≥1 of these CV conditions or risk factors	36 (84)	36 (88)	17 (85)	36 (86)	35 (81)	18 (78)
Hypertension	30 (70)	30 (73)	15 (75)	32 (76)	30 (70)	16 (70)
Dyslipidemia	24 (56)	21 (51)	13 (65)	18 (43)	20 (47)	7 (30)
Diabetes mellitus	13 (30)	8 (20)	5 (25)	11 (26)	10 (23)	3 (13)
Cardiac arrhythmia	10 (23)	5 (12)	6 (30)	10 (24)	4 (9)	1 (4)
Coronary artery disease	9 (21)	10 (24)	6 (30)	5 (12)	6 (14)	3 (13)
Cardiac failure/left ventricular dysfunction	8 (19)	4 (10)	4 (20)	4 (10)	4 (9)	2 (9)
Peripheral vascular disease	3 (7)	2 (5)	2 (10)	4 (10)	4 (9)	1 (4)
Cerebrovascular disease	3 (7)	2 (5)	0	1 (2)	1 (2)	1 (4)
Obesity (BMI ≥30)	29 (67)	27 (66)	14 (70)	21 (50)	28 (65)	10 (43)[c]
Chronic kidney disease[d]	12 (28)	13 (32)	6 (30)	14 (33)	12 (29)[c]	3 (13)
Sleep apnea syndrome	6 (14)	5 (12)	3 (15)	2 (5)	4 (9)	3 (13)
Venous thromboembolic disease	1 (2)	1 (2)	1 (5)	2 (5)	1 (2)	1 (4)

Abbreviations: BMI, body mass index; CV, cardiovascular.
SI conversion factor: To convert uric acid to μmol/L, multiply by 59.485.
[a] Self-reported.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Indicates 1 missing value.
[d] Chronic kidney disease was defined as a creatinine clearance of less than 60 mL/min calculated with the Cockcroft-Gault equation.[33]

Table 2. End-Point Analyses for Primary and Secondary Outcomes (Pooled Modified Intent-to-Treat)[a]

	Pegloticase Biweekly	Pegloticase Monthly	Placebo
	Primary End Point		
No. responders/No. treated (%) [95% CI][b]			
Pooled results	36/85 (42) [32 to 54]	29/84 (35) [24 to 46]	0/43 (0) [0 to 8]
P value[c]	<.001	<.001	
Trial C0405	20/43 (47) [31 to 62]	8/41 (20) [9 to 35]	0/20 (0) [0 to 17]
P value[c]	<.001	.04	
Trial C0406	16/42 (38) [24 to 54]	21/43 (49) [33 to 65]	0/23 (0) [0 to 15]
P value[c]	.001	<.001	

(continued)

Table 2. End-Point Analyses for Primary and Secondary Outcomes (Pooled Modified Intent-to-Treat)[a] (continued)

	Pegloticase Biweekly	Pegloticase Monthly	Placebo
	Secondary End Points		
Resolution of ≥1 tophi, No. patients/No. evaluable patients (%) [95% CI]	21/52 (40) [27 to 55]	11/52 (21) [11 to 35]	2/27 (7) [1 to 24]
P value[c]	.002	0.20	
Flare incidence, No. patients/No. treated (%) [95% CI]			
Months 1-3	64/85 (75) [65 to 84]	68/84 (81) [71 to 89]	23/43 (53) [38 to 69]
P value[c]	.02	.002	
Months 4-6	28/69 (41) [29 to 53]	39/69 (57) [44 to 68]	29/43 (67) [51 to 81]
P value[c]	.007	.32	
Flare frequency, No. flares per patient			
Months 1-3, mean (SD)	2.3 (2.1) (n = 85)	2.7 (2.4) (n = 84)	1.2 (1.6) (n = 43)
[95% CI] (quartiles)	[1.8 to 2.7] (1, 2, 4)	[2.2 to 3.2] (1, 2, 4)	[0.7 to 1.7] (0, 1, 2)
P value[d]	.001	<.001	
Months 4-6, mean (SD)	0.8 (1.2) (n = 69)	1.5 (2.0) (n = 69)	1.3 (1.5) (n = 43)
[95% CI] (quartiles)	[0.5 to 1.1] (0, 0, 1)	[1.1 to 2.0] (0, 1, 3)	[0.8 to 1.7] (0, 1, 2)
P value[d]	.06	.45	
Tender joints, No. per patient			
Baseline mean (SD)	11.7 (13.0) (n = 84)	11.1 (13.5) (n = 83)	14.1 (14.8) (n = 43)
[95% CI] (quartiles)	[8.9 to 14.5] (1, 7, 18.5)	[8.1 to 14.0] (1, 4, 16)	[9.6 to 18.7] (3, 9, 21)
P value[d]	.36	.26	
Change at final visit, mean (SD)	–7.4 (11.9) (n = 78)	–6.1 (10.6) (n = 77)	–1.2 (12.3) (n = 43)
[95% CI] (quartiles)	[–10.1 to –4.7] (–9, –3, 0)	[–8.6 to –3.7] (–11, –3, 0)	[–5.0 to –2.6] (–6, –1, 3)
P value[d]	.01	.03	
Swollen joints, No. per patient			
Baseline, mean (SD)	8.9 (11.1) (n = 84)	10.1 (10.0) (n = 83)	13.2 (13.7) (n = 43)
[95% CI] (quartiles)	[6.5 to 11.3] (1, 5, 10)	[7.9 to 12.2] (2, 7, 15)	[8.9 to 17.4] (2, 11, 18)
P value[d]	.08	.19	
Change at final visit, mean (SD)	–5.5 (10.5) (n = 78)	–5.1 (7.8) (n = 77)	–2.6 (11.6) (n = 43)
[95% CI] (quartiles)	[–7.9 to –3.2] (–8, –2.5, 0)	[–6.9 to –3.3] (–7, –3, 0)	[–6.2 to 1.0] (–6, –2, 0)
P value[d]	.18	.22	
HAQ-DI score[e]			
Baseline, mean (SD)	1.10 (0.86) (n = 83)	1.21 (0.86) (n = 84)	1.24 (0.95) (n = 43)
[95% CI] (quartiles)	[0.92 to 1.29] (0.25, 1.00, 1.88)	[1.02 to 1.39] (0.38, 1.12, 2.00)	[0.94 to 1.53] (0.25, 1.12, 2.12)
P value[d]	.43	.86	
Change at final visit, mean (SD) (MCID ≥0.22)	–0.22 (0.64) (n = 77)	–0.20 (0.55) (n = 78)	0.02 (0.41) (n = 43)
[95% CI] (quartiles)	[–0.37 to –0.08] (–0.50, –0.12, 0.00)	[–0.32 to –0.07] (–0.50, –0.06, 0.00)	[–0.11 to 0.15] (–0.12, 0.00, 0.25)
P value[d]	.01	.01	
HAQ pain score[f]			
Baseline, mean (SD)	44.2 (27.7) (n = 84)	45.1 (27.0) (n = 84)	53.9 (28.1) (n = 43)
[95% CI] (quartiles)	[38.2 to 50.2] (21.5, 45.0, 68.0)	[39.2 to 50.9] (21.0, 50.0, 63.5)	[45.3 to 62.5] (29.0, 58.0, 75.0)
P value[d]	.07	.09	
Change at final visit, mean (SD) (MCID ≥10)	–11.4 (33.8) (n = 78)	–6.9 (27.0) (n = 78)	1.4 (30.0) (n = 43)
[95% CI] (quartiles)	[–19.1 to –3.8] (–37.0, –8.0, 8.0)	[–13.0 to –0.8] (–22.0, –2.5, 8.0)	[–7.9 to 10.6] (–15.0, –1.0, 14.0)
P value[d]	.03	.14	
SF-36 Physical Component Summary score[g]			
Baseline, mean (SD)	35.2 (10.9) (n = 83)	33.3 (9.8) (n = 84)	31.0 (11.1) (n = 43)
[95% CI] (quartiles)	[32.8 to 37.5] (27.1, 33.3, 43.1)	[31.1 to 35.4] (26.2, 33.1, 40.3)	[27.6 to 34.4] (22.0, 27.8, 39.3)
P value[d]	.05	.26	
Change at final visit, mean (SD) (MCID ≥2.5)	4.4 (9.4) (n = 77)	4.9 (8.5) (n = 77)	–0.3 (9.0) (n = 43)
[95% CI] (quartiles)	[2.3 to 6.5] (–1.2, 3.1, 9.9)	[3.0 to 6.9] (–0.1, 3.0, 10.5)	[–3.1 to 2.5] (–4.0, –0.1, 3.1)
P value[d]	.01	.002	

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.

SI conversion factor: To convert uric acid to μmol/L, multiply by 59.485.

[a] Pooled data from the 2 replicate studies. As prespecified, 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 3.[34-36]

[f] Pain was scored from 0 to 100 mm on the HAQ visual analog scale.

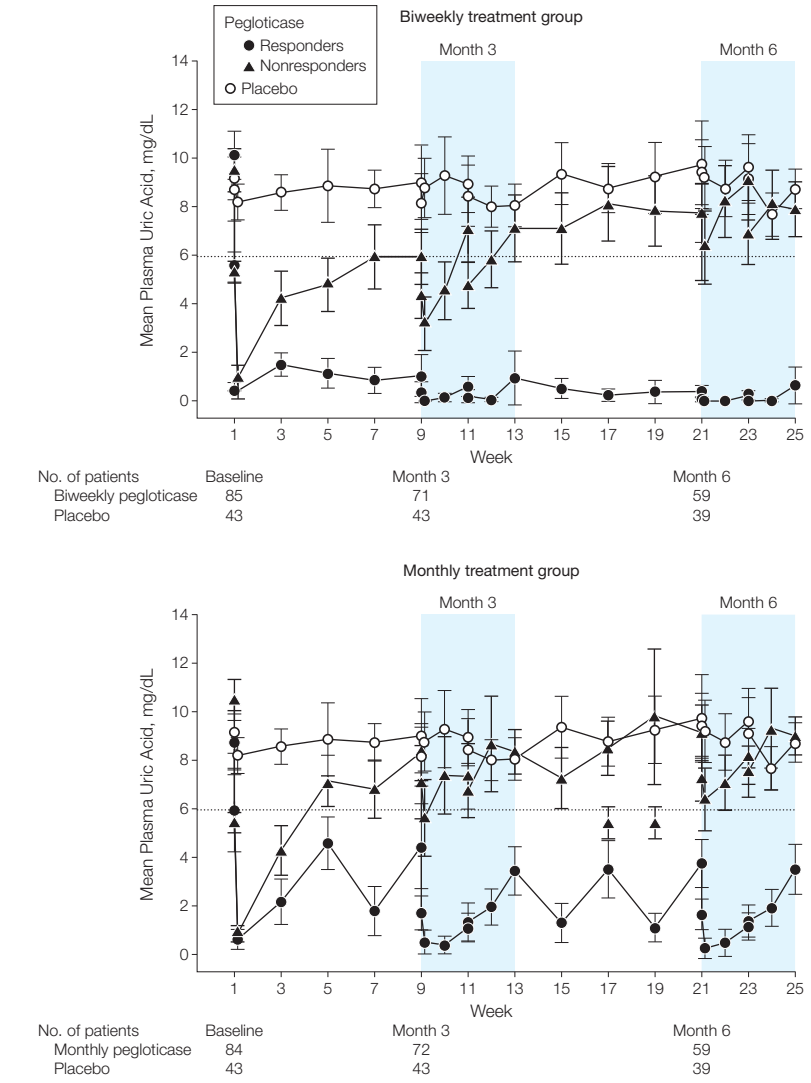
[g] SF-36 evaluates 12 domains spanning physical and mental components.[12,36,37]

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.[38] 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. Other 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.

Three APTC events were identified by the adjudication committee: 2 CV

Figure 2. Plasma Uric Acid Levels During Treatment Period for Patients Receiving Biweekly or Monthly Pegloticase Treatment



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.

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.

Table 3. Number of Pooled Replicate Modified Intent-to-Treat Group Patients Experiencing Treatment-Emergent Adverse Events[a]

Event	No. (%) of Patients		
	Pegloticase Biweekly (n = 85)	Pegloticase Monthly (n = 84)	Placebo (n = 43)
Any AE	80 (94)	84 (100)	41 (95)
Any serious AE	20 (24)	19 (23)	5 (12)
Death[b]	2 (2)	1 (1)	0
Discontinuation owing to AE	15 (18)	16 (19)	1 (2)
Most commonly reported[c]			
Gout flare	65 (76)	71 (85)	35 (81)
Infusion reaction	22 (26)	35 (42)	2 (5)
Headache	8 (9)	9 (11)	4 (9)
Nausea	10 (12)	6 (7)	1 (2)
Back pain	3 (4)	7 (8)	2 (5)
Nasopharyngitis	6 (7)	4 (5)	1 (2)
Dyspnea	4 (5)	5 (6)	2 (5)
Vomiting	4 (5)	5 (6)	1 (2)
Chest pain	5 (6)	4 (5)	1 (2)
Pruritus	3 (4)	5 (6)	0
Contusion	7 (8)	0	1 (2)
Pyrexia	2 (2)	5 (6)	1 (2)
Constipation	5 (6)	2 (2)	2 (5)
Blood pressure increased	0	6 (7)	0
Adjudicated CV events			
APTC events	2 (2)	1 (1)	0
CV death	2 (2)	0	0
Nonfatal MI	0	1 (1)[d]	0
Non-APTC events	3 (2)[e]	6 (7)	0
CHF	2 (2)	1 (1)	0
Arrhythmia	1 (1)	1 (1)	0
DVT	0	1 (1)	0
TIA	0	1 (1)	0
Unstable angina	0	1 (1)	0
Coronary revascularization	0	1 (1)	0

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.

[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.

[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.

[c] The most commonly reported AEs were defined as those occurring in ≥5% of patients in any treatment group and at least 1% more frequently in patients treated with pegloticase compared with patients receiving placebo.

[d] One patient had an APTC event (nonfatal myocardial infarction) and a non-APTC event (coronary revascularization), both recorded here.

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

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. The

significant disease-modifying benefits of pegloticase given every 2 weeks (tophus resolution, reduced flare frequency, reduction in TJC, and improved patient-reported outcomes in pain, physical function, and QOL) were demonstrable within 6 months, a time frame unique in randomized controlled 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 physical function and QOL scores exceeding the minimal clinically important difference in pegloticase-treated patients, coupled with deterioration in pain and QOL in placebo-treated patients, provide evidence that chronic elevations in UA are associated with significant functional impairment as measured by several criteria. This relationship has previously been difficult to distinguish from functional impairment imparted by serious comorbidities that typically characterize gout patients, and therefore, the ability of pegloticase to improve patient reported outcomes in this context is noteworthy.

Infusion-related reactions, including some cases fulfilling criteria for anaphylaxis, 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 administration of pegloticase in clinical practice.[19] In our post hoc analysis, we observed that most (79%) pegloticase-treated patients experiencing IRs in the course of development of high titers of pegloticase antibody did so only after an associated loss of the urate-lowering response to pegloticase. Since all patients in this study received routine prophylaxis for IRs, including glucocorticoids, the extent to which this regimen may have mitigated the frequency and severity of IRs is uncertain. Nevertheless, it would seem prudent to maintain IR prophylaxis in all individuals receiving pegloticase therapy.

A relatively small number of mechanistically diverse albeit serious CV AEs occurred during this study. Despite the 4-fold greater number of patients receiving pegloticase vs placebo, the elevated CV risk profile of this population, and the absence of a compelling mechanism connecting pegloticase with CV AEs,[39] the observed numerical imbalance 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 comorbidities prior to and during pegloticase treatment would be appropriate.

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Author Contributions: Dr Becker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Horowitz, Maroli, Becker.

Conflict of Interest Disclosures: Drs Horowitz, Huang, Maroli, and Waltrip were employees of Savient Pharmaceuticals at the time of conception and performance of the reported study. Dr Sundy reported receiving fees for consulting and grants from Savient Pharmaceuticals, Ardea Biosciences, Nuon Therapeutics, Regeneron, and Novartis and payment for lectures, including service on the speakers' bureau, for Takeda Pharmaceuticals North America. While Duke University, Dr Sundy's institution, may receive royalties as a result of the licensing agreement with Savient 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 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 consulting fees and/or pending clinical trial grants from Ardea Biosciences, Nuon Therapeutics, Regeneron, Novartis, URL/Mutual Pharmaceuticals, and Takeda Pharmaceuticals. Dr Yood reported 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 serving as an investigator for a clinical trial sponsored by Takeda Pharmaceuticals North America, for which a grant was paid to his institution. Dr Edwards reported consulting income from Savient Pharmaceuticals, Takeda Pharmaceutical North America, Ardea Biosciences, Novartis, 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 expense reimbursement from Savient; and owning stock in Savient that was purchased through a commercial vendor. Dr White reported receiving consulting fees for chairing the CV Adjudication Committee and for participation in the FDA Arthritis Advisory Committee meeting on pegloticase. Dr Lipsky 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. 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 company at the time of this submission. Dr Huang reported consulting for Ardea Biosciences in 2010 after leaving Savient Pharmaceuticals and currently holding stock and/or stock options in Savient. Dr Maroli reported holding stock and stock options in Savient at the time the study was performed and analyzed but having no financial interest in the company at the time of this submission. Dr Waltrip reported consulting for Ardea Biosciences in 2010 after leaving Savient Pharmaceuticals. Dr Hamburger is currently an employee of Savient Pharmaceuticals and reported currently holding stock and/or stock options in Savient. Dr Becker 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; receiving fees from Takeda Pharmaceuticals, BioCryst Pharmaceuticals, Ardea Biosciences, Metabolex, URL/Mutual Pharmaceuticals, and Regeneron for consultation regarding research and development of gout-related products; and receiving fees from UpToDate, where he edits the section on crystal-induced arthritis. No other authors reported conflicts.

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Laboratories, and ICON Laboratories (the central laboratory 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 sponsor author-employees and immediately presented for critical review and interpretation to the participating academic authors. Additional reviews of immunologic and cardiovascular data were carried out by academic authors with specific expertise 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 intellectual content The academic authors determined 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.

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