Pegloticase in Combination With Methotrexate in Patients With Uncontrolled Gout: A Multicenter, Open-label Study (MIRROR)

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ABSTRACT. Objective. To examine the efficacy and safety of pegloticase in combination with methotrexate (MTX) in patients with uncontrolled gout in an exploratory, open-label clinical trial (ClinicalTrials.gov: NCT03635957) prior to a randomized, controlled trial.

Methods. A multicenter, open-label efficacy and safety study of pegloticase with MTX co-treatment was conducted in patients with uncontrolled gout. Patients were administered oral MTX (15 mg/week) and folic acid (1 mg/day) 4 weeks prior to and throughout pegloticase treatment. The primary study outcome was the proportion of responders, defined as serum uric acid (sUA) < 6 mg/dL for ≥ 80% of the time during Month 6 (Weeks 20, 22, and 24). All analyses were performed on a modified intent-to-treat population, defined as patients who received ≥ 1 pegloticase infusion.

Results. Seventeen patients were screened and 14 patients (all men, average age 49.3 ± 8.7 years) were enrolled. On Day 1, mean sUA was 9.2 ± 2.5 mg/dL, and 12 of the 14 patients had visible tophi. At the 6-month timepoint, 11/14 (78.6%, 95% CI 49.2–95.3%) met the responder definition, with 3 patients discontinued after meeting protocol-defined treatment discontinuation rules (preinfusion sUA values > 6 mg/dL at 2 consecutive scheduled visits). All patients tolerated MTX. No new safety concerns were identified.

Conclusion. In this study, an increased proportion of patients maintained therapeutic response at 6 months when treated concomitantly with MTX and pegloticase as compared to the previously reported 42% using pegloticase alone. These results support the need for a randomized study of MTX or placebo with pegloticase to validate these open-label findings.

Key Indexing Terms: gout, methotrexate, pegloticase, tophi, uricase

Gout affects an estimated 9.2 million people (3.9% of adults) in the United States1 and occurs when serum uric acid (sUA) levels chronically remain above the solubility limit (6.8 mg/dL). Though typically thought of as an "articular disease," monosodium urate crystals result in chronic inflammation throughout the body, even when patients are asymptomatic.2,3 Urate deposits and chronic inflammation may negatively affect soft tissues4 and other organs, as evidenced by associations between hyperuricemia and hypertension,5,6 cardiovascular (CV) disease,7,8,9,10,11 diabetes,5,12 kidney disease,13,14 and death.11,15,16 The American College of Rheumatology 202017 and the European League Against Rheumatism18 guidelines recommend maintaining sUA levels below 6 mg/dL. Unfortunately, urate-lowering therapies (ULTs) are often underutilized, and a small subset of patients with gout cannot tolerate or do not respond to them.19 Consequently, sUA levels remain > 6 mg/dL and urate deposition continues,20

This work was supported by Horizon Therapeutics.

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JKB has received research support from Horizon Therapeutics andRadius Health as a study site and principal investigator. He has received consulting/speaker fees > $10k from Horizon Therapeutics, Celgene, Novartis, and AbbVie. JRT has received research grants/support from Horizon. HMK has received research support from Horizon Therapeutics as a study site and principal investigator, and has served as a speaker. PMP, KO, and BL are employees of and own stock in Horizon Therapeutics. MEW has received grants from Amgen, Bristol Myers Squibb, Crescendo Bioscience, Lilly, and Sanofi; has received consulting fees > $10k from Bristol Myers Squibb, Corova, and Lilly and < 10k from AbbVie, Amgen, Arena, GlaxoSmithKline, Gilead Sciences, Horizon Therapeutics, Lycera, Novartis, Pfizer, Roche, Samsung, Scipher Medicine, and Set Point; and has stock options in Lycera, Can-Fite BioPharma, Scipher Medicine, Inmedix, and Versa. JP has received research support from Horizon Therapeutics (study site/investigator), and has also served as an advisor and speaker for Horizon Therapeutics. RB has no financial relationships that pose a potential conflict of interest.

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Accepted September 11, 2020.
with an estimated 10% of patients developing chronic tophi-
caceous gout.21 Patients with treatment-failure gout have a lower
quality of life and significant disability, particularly with respect
to physical functioning.22

Pegloticase (pegylated uricase) is a medication approved by
the US Food and Drug Administration that is highly effective
in lowering sUA by converting uric acid to allantoin, which
is readily excreted by the kidneys. However, clinical studies have
shown that only 42% of patients maintain sUA below 6.0 mg/
dL over 6 months of pegloticase therapy, with 26% of patients
having infusion-related reactions (IRs) in the absence of uric
acid monitoring during treatment.23,24 Both loss of efficacy and
IRs have been attributed to development of antidrug antibodies
(ADAs) that accelerate pegloticase clearance.25,26,27 Because treat-
ment options for patients with uncontrolled gout are limited,
some physicians have coadministered immunomodulators with
pegloticase in an effort to prevent ADA formation and increase
the length of effective pegloticase therapy, similar to what is
done in other rheumatic diseases treated with biologics.28,29 Case
reports support the successful use of immunomodulators (meth-
otrexate [MTX], azathioprine [AZA], leflunomide [LEF], and
cyclosporine A [CSA]) with pegloticase.30,31–37 However, these
studies are limited and examined different immunomo-
dulatory agents with varying doses, schedules, and routes.
In the current MTX/pegloticase case series, the proportion of
responders (based on each study’s definition) was 100% (10/10
patients),33 100% (7/7 patients),33,34 and 80% (8/10 patients),35
all of which were higher than the 42% rate observed in clinical
trials.23 Given the promising clinical case series with MTX, the
current study prospectively examined the efficacy and safety of
pegloticase-MTX cotherapy in subjects with uncontrolled gout.

MATERIALS AND METHODS
This multicenter, open-label efficacy and safety study (ClinicalTrials.gov:
NCT03653957) was conducted at 6 sites in the US. The trial was reviewed
and approved for all sites by the Western Institutional Review Board
(Puyallup, Washington; approval number 20182156). All subjects provided
written informed consent to participate in the trial, and all study conduct
adhered to the Declaration of Helsinki.

Study population. Men and women between 18 and 65 years of age with
uncontrolled gout were considered for inclusion. Uncontrolled gout was
defined as an sUA ≥ 6 mg/dL prior to beginning study treatment (peglot-
icase) and at least 1 of the following: inability to maintain sUA < 6 mg/dL on
other urate-lowering therapies (ULT), intolerance to current
ULT, or functionally limiting tophaceous deposits (detected clinically or
with dual-energy computed tomography). Patients were excluded from
participation if any of the following were true/present: serious acute bacte-
rial infection (< 2 weeks prior), severe chronic/recurrent bacterial infection,
immunocompromised status, glucose-6-phosphate dehydrogenase (G6PD)
deficiency (tested at screening), severe chronic renal impairment (glomer-
ular filtration rate [GFR] < 25 mL/min/1.73 m² or currently on dialysis), or
current liver disease (alanine aminotransferase [ALT] or aspartate amin-
otransferase [AST] > 3 times upper limit of normal). See Supplementary
Table 1 (available with the online version of this article) for the complete
list of inclusion and exclusion criteria.

Study medications. All patients were to receive MTX and pegloticase.
A study design schematic is shown in Figure 1. Briefly, subjects were screened
for eligibility prior to beginning the 4-week MTX run-in period (Week −4
through Day 1), during which subjects received 15 mg/week of oral MTX
and 1 mg/day oral folic acid. The MTX dose was chosen based on several
factors. First, a trial examining MTX/adalimumab combination therapy for
rheumatoid arthritis found that a dose of at least 10 mg/week was needed to
maximize serum adalimumab concentrations.38 Second, an article reporting
expert opinion, based on a systematic literature review and input from
751 rheumatologists in 17 countries, recommends a starting oral MTX
dose of 10–15 mg/week.39 Third, rheumatologists consulted during trial
design recommended a dose of 15 mg/week. Finally, the safety results from
the Cardiovascular Inflammation Reduction Trial were reassuring with
respect to an MTX dose of 15–20 mg/week in a population with similar
comorbidities.40

During the treatment period (maximum 52 weeks), patients continued
weekly MTX and daily folic acid, and initiated pegloticase treatment (8 mg
intravenous [IV] pegloticase every 2 weeks). Starting ≥ 1 week prior
to Day 1, all patients were required to start gout flare prophylaxis regimen:
colchicine and/or nonsteroidal antiinflammatory drugs (NSAIDs) and/
or low-dose prednisone ≤ 10 mg/day (physician discretion on choice and
dose of therapy). All patients continued flare prophylaxis for the greater of 6
months, 3 months after sUA was first < 6 mg/dL (nontophaceous patients),
or 6 months after sUA was first < 5 mg/dL (tophaceous patients).41
Flares could be treated with NSAIDs, colchicine, corticosteroids, and
intraarticular steroid injections as clinically indicated. Additionally, patients
completed standard infusion reaction prophylaxis prior to each pegloticase
infusion: oral fexofenadine (60 or 180 mg based on physician discretion)
the day before and morning of, acetaminophen (paracetamol; 1000 mg)
the morning of and IV glucocorticoids (200 mg hydrocortisone or 125 mg
methylprednisolone over 10–30 minutes) immediately prior to pegloticase
infusion.

Pegloticase uric acid monitoring protocol42 was followed to minimize
the occurrence of IRs. Briefly, patients who had an sUA level > 6 mg/dL at 2
consecutive study visits after Week 2 discontinued therapy.

Screening. Patients were consented and eligibility was confirmed.
Demographic, medical/surgical history, and current medication/substance
use information was collected. Patients underwent physical exam, and
gout flares in the last 2 weeks were assessed. Blood and urine samples were
collected for laboratory testing, which included sUA measurement, hemato-
logy, and clinical chemistry panels.

MTX run-in period. Patients initiated MTX within 2 weeks of screening.
Immediately prior to MTX initiation (–4 weeks), patients underwent study
eligibility reassessment, medical/surgical history update, and medication/
substance use update. Physical, laboratory, and gout flare assessments were
repeated. Adverse events (AEs) were assessed. Patients returned for a study
visit 2 weeks later.

Pegloticase/MTX treatment period. All patients were to receive treatment
with both pegloticase and MTX from Day 1 through the end of the treat-
ment period (maximum of 52 weeks). Follow-up visits occurred every
2 weeks between Day 1 and Week 52. The full schedule of assessments is
found in Supplementary Table 2 (available with the online version of this
article). Briefly, general study visits and safety assessments included AE
assessment, concomitant medication update, and physical examination.
Blood and urine samples were collected, including a blood sample just prior
to each pegloticase infusion for sUA measurement.

AEs were graded using established criteria for rheumatology clinical
trials (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening event).42 Gout
flare determinations were made using a standardized definition (yes to 3 of
4): Had a gout flare occurred since the last visit; if yes to flare, was pain in
joints different than normal, was pain at rest > 3 out of 10 (0 = no pain, 10
= worst pain imaginable), and had joint swelling occurred.43

Study endpoints. The primary endpoint was the proportion of pegloticase
responders during Month 6 (Weeks 20, 22, and 24). Patients were consid-
ered responders if they had sustained normalization of sUA (< 6 mg/dL) for
at least 80% of the time during Month 6.

Secondary endpoints included the proportion of pegloticase responders

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RESULTS

A total of 17 patients were screened for study inclusion between September 26, 2018, and April 2, 2019, with 15 patients starting MTX treatment. Fourteen patients completed the MTX run-in period. One patient began MTX treatment but was lost to follow-up after Week –2; this patient is included in the ITT population but not the mITT population. Fourteen patients completed the MTX run-in period, administered over the first 24 weeks of pegloticase + MTX treatment, and 11 patients (78.6%) completed all 12 scheduled pegloticase infusions. During this treatment period, the mean weekly dose of MTX was 14.7 ± 1.1 mg/week. All 14 patients in the mITT population were initially administered hydrocortisone for pre-infusion prophylaxis (2 patients received only 100 mg for the first 3 and 6 infusions). Two patients were switched to methylprednisolone (prior to infusion 8 and 10).

Patients were administered a mean total MTX dosage of 64.4 ± 7.7 mg (range 60–75) during the MTX run-in period; no patients had a dosage reduction from the planned 15 mg/week. An average of 10 pegloticase infusions (range 2–12) were administered over the first 24 weeks of pegloticase + MTX treatment, and 11 patients (78.6%) completed all 12 scheduled pegloticase infusions. During this treatment period, the mean weekly dose of MTX was 14.7 ± 1.1 mg/week. All 14 patients in the mITT population were initially administered hydrocortisone for pre-infusion prophylaxis (2 patients received only 100 mg for the first 3 and 6 infusions). Two patients were switched to methylprednisolone (prior to infusion 8 and 10).

Study outcomes. A complete list of efficacy outcomes is provided in Table 2. Briefly, 11 of 14 patients (78.6%, 95% CI 49.2–95.3%) in the mITT population met the primary endpoint. Three patients who were not considered responders
stopped treatment after meeting pegloticase discontinuation criteria. Loss of response happened relatively early, with 1 patient discontinuing after 2 infusions and 1 patient after 3 infusions. The third patient discontinued treatment after 5 infusions.

The proportion of responders during Month 3 and overall (Months 3 and 6 combined) was also 78.6% (95% CI 49.2–95.3%). With a stricter sUA response criteria of < 5 mg/dL for at least 80% of the time during Month 3, Month 6, and overall, the proportion of responders at 78.6% for all 3 time periods (Table 2). Mean sUA rapidly decreased after the first pegloticase infusion and remained low through Week 24 (Figure 2A). The sUA change from baseline was −9.0 ± 2.8 mg/dL at both Week 14 and 24 (n = 11). Prior to pegloticase/MTX co-therapy, the 14 patients had 6.4 ± 7.9 joints affected by tophi (median 4, range 0–31), and the mean number of joints affected by tophi at their last assessment was 2.6 ± 3.5 (median 1, range 0–12).

Safety. Ten of 15 patients (66.7%) in the ITT population who were administered MTX during the run-in period experienced 1 or more AEs (Table 3). The most commonly observed AEs during the run-in period were gout flare, nausea, and abdominal discomfort. During the co-treatment period, all patients experienced 1 or more AEs. The most commonly observed AEs were gout flare (12 patients [85.7%]), diarrhea (3 patients [21.4%]), and upper respiratory tract infection (3 patients [21.4%]).

AEs of special interest included IR, anaphylaxis, CV events, and gout flare (Table 4). An IR in 1 patient was reported by an investigator. The event was described as a mild cough (approximately 1 hour in duration) that occurred during the fifth pegloticase infusion. The sUA was not elevated (1.0 mg/dL 2 days prior to infusion 5), and the patient completed the 24-week treatment period as a responder. Because sUA levels remained very low and there were no typical signs of an IR (e.g., hives, itchiness, shortness of breath, sweating, fever/chills), the study sponsor did not consider the event to be an IR. Anaphylaxis was not observed in any patient. Gout flares occurred in 12 patients (85.7%) during the co-treatment period and, with the exception of 2 severe flares (grade 3), all were mild to moderate in intensity (grade 1–2, Rheumatology Common Toxicity Criteria v.2.04). Less than one-third of flares required glucocorticoid treatment. Twelve patients (85.7%) experienced a mean of 4.3 ± 2.2 flares (range 1–8) during the first 12 weeks of pegloticase therapy (Table 4). During Weeks 12 to 24, five of the 11 patients (45.5%) who remained on therapy experienced a mean of 3.0 ± 2.6 flares (range 1–7; Table 4). In the 11 patients who completed 24 weeks of therapy, 75% of flares occurred in the first 12 weeks.

No patient experienced a major adverse CV event (includes nonfatal myocardial infarction, nonfatal stroke, CV death, and congestive heart failure) and no deaths occurred. One case of bacterial sepsis secondary to cholecystitis occurred (investigator deemed this unrelated to trial medications) and was classified as a serious AE.

In the run-in period, there was an initial relatively minor and not unexpected increase in liver function tests followed by stabilization (Figure 2B). Prior to the first MTX dose, 3 of 14 patients had an ALT above the upper limit of normal (ULN), and 2 of 14 patients had an AST above the ULN. During the treatment period, 7 patients had ALT levels above the ULN (all with 2 or more values ≥ ULN), and 7 patients had an AST above the ULN (6 with 2 or more values ≥ ULN) at any time postbaseline.

Two patients had an MTX dose reduction during the co-treatment period. One was inadvertent (took 12.5 mg instead of 15 mg on 2 occasions). One patient had a reduction to 10 mg/week in response to AEs (leukopenia [2.5 × 10^9/L], neutropenia [1.0 × 10^9/L], elevated ALT [90 U/L]). These AEs resolved; however, the patient continued at the lower dose.

Thirteen of 14 patients (92.9%) maintained or had an improvement in CKD status. One patient went from CKD stage 2 to 3A with an eGFR of 61 mL/min/1.73 m^2 at screening, 76 mL/min/1.73 m^2 at the start of MTX, and 58 mL/min/1.73 m^2 at study conclusion.

**DISCUSSION**

All biologic medications can engender ADAs in patients that receive them.⁴⁴ The degree of ADA response varies according to the biologic therapy administered.⁴⁴ MTX or azathioprine use in patients receiving biologics has been shown to minimize the development of ADAs across a wide variety of disease states. In autoimmune conditions, if disease-modifying anti-rheumatic drugs (DMARDs) are ineffective, a biologic can be initiated with the DMARD continuing in combination. The absence of ADAs to biologics correlates with longer therapy duration, better efficacy response, and fewer AEs, including IRs.⁴⁵⁶⁷

Pegloticase has well-established efficacy, but duration of response is limited in some patients due to the development of ADAs that primarily bind to the molecule’s polyethylene glycol.
The presence of ADAs has been shown to coincide with increasing sUA levels in patients on therapy. Elevated sUA, therefore, serves as a biomarker for loss of therapeutic efficacy and an increased risk of IRs. Since immunomodulating therapies are not part of standard gout care, unlike other biologics, pegloticase has been used historically as monotherapy.

In an effort to help more patients with uncontrolled gout complete a full course of therapy, some clinicians have
Table 3. Adverse events (AEs) observed during the MTX run-in and pegloticase + MTX treatment periods.

<table>
<thead>
<tr>
<th>AEs occurring in &gt; 1 patient in either period</th>
<th>MTX Run-in Period, N = 15</th>
<th>Pegloticase + MTX Period, mITT Population, N = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout flare</td>
<td>5 (33.3)</td>
<td>12 (85.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (6.7)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Muscle strain</td>
<td>0</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (13.3)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (13.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are expressed in n (%). ITT: intent-to-treat (any patient exposed to MTX during the run-in period); mITT: modified intent-to-treat (any patient exposed to pegloticase during the pegloticase + MTX treatment period); MTX: methotrexate.

Table 4. Adverse events of special interest.

<table>
<thead>
<tr>
<th>Subjects experiencing gout flare, N = 14</th>
<th>Pegloticase + MTX Period, mITT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions, no. patients/no. treated (%)</td>
<td>1/14 (7.1)*</td>
</tr>
<tr>
<td>Anaphylaxis, no. patients/no. treated (%)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>Cardiovascular events, no. patients/no. treated (%)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>Subjects experiencing gout flare, no. patients/no. treated (%)</td>
<td>12/14 (85.7)</td>
</tr>
</tbody>
</table>

* The investigator reported infusion reaction as a mild cough, occurring during the 5th infusion and lasting for 1 h, not accompanied by other signs and symptoms and not requiring specific intervention. a 11 subjects remained on pegloticase + MTX therapy during Week 12 to Week 24. mITT: modified intent-to-treat; MTX: methotrexate; no: number.

administered immunomodulation co-treatment with pegloticase. The most studied agent has been MTX, but AZA, LEF, and CSA have also shown improved pegloticase response rates, compared to the 42% observed in phase III clinical trials. Botson and Peterson showed a 100% response rate in 10 patients co-treated with oral MTX; Albert, et al showed an 80% response rate in 10 patients co-treated with oral or subcutaneous MTX; and Bessen, et al showed a 100% response rate in 7 patients co-treated with MTX. Two additional cases reported successful pegloticase therapy with other immunomodulators (1 case of AZA use, 1 case of chronic mycophenolate mofetil and CSA use in a heart transplant patient), highlighting the potential of immunomodulation to increase the pegloticase responder rate.

This prospective, open-label clinical trial sought to evaluate the ability of MTX given concomitantly with pegloticase to enhance the response rate seen with pegloticase alone. All included patients were treated with oral MTX and folic acid for 4 weeks prior to and throughout pegloticase therapy. With this protocol, 11 of 14 uncontrolled gout patients (78.6%) were responders to pegloticase during Month 6. Three patients had a loss of pegloticase response during the study, as indicated by persistently elevated sUA, and therapy was discontinued.

The most common AE observed was gout flares (85.7% of patients). This flare occurrence was similar to the 76% rate observed in phase III trials. In the current trial, 75% of flares were observed in the first 3 months of pegloticase therapy, with a reduction in flares observed beyond the first 3 months of treatment. One serious AE of bacterial sepsis occurred; it resolved, and the site investigator determined it unrelated to the study drug. Other AEs occurring in > 1 patient included diarrhea, respiratory tract infection, sinusitis, muscle strain, and hypertension. Patients experiencing diarrhea were also receiving colchicine at the time of the AE.

All patients tolerated MTX coadministered with pegloticase, and no new safety concerns with combined therapy were identified. Given that pegloticase has not been found to have drug interactions with any other medical therapy, this was not surprising. The effects of MTX on pegloticase pharmacokinetics (PK) and immunogenicity were evaluated using PK measures (including pegloticase serum concentration) and ADA levels, respectively. These analyses are ongoing and will be an important piece to understand the mechanisms by which MTX is beneficial in those undergoing pegloticase therapy. The clinical findings stand on their own and will not be changed by the full knowledge of PK and immunogenicity data. Given the dramatic departure in response rates from the original phase III program without MTX, we felt it prudent to report the study’s primary efficacy outcome along with the safety findings now.

This study had several limitations, including its small sample size, open-label design, and lack of a comparator group. However, this small uncontrolled study does demonstrate that a higher percentage of patients treated with MTX plus pegloticase achieved sustained sUA levels < 6 mg/dl than the previously found 42% of patients treated with pegloticase alone. These results inform the need to test pegloticase plus MTX vs
pegloticase plus placebo in a controlled trial. Such a trial would also confirm that the responder rate increase resulted from MTX use and that these findings were not confounded by other factors, including differences in steroid prophylactic agents (methylprednisolone vs hydrocortisone\(^\text{6,7}\)). Therefore, a randomized, double-blind, placebo-controlled (pegloticase with placebo) efficacy and safety study is currently ongoing (MIRROR RCT, ClinicalTrials.gov: NCT03994731) to address these limitations.

In conclusion, pegloticase is indicated for chronic gout in patients refractory to conventional therapy. The ability of pegloticase to dramatically lower sUA and ultimately overall urate burden, in those patients who have no other options, creates a unique, singular opportunity for treatment that is only limited by the treatment response rate. Paramount is any mechanism that can improve the pegloticase response rate and provide an opportunity to further fulfill the unmet need. In the current study, the markedly increased pegloticase response rate observed with immunomodulation agrees and substantiates those found in previously reported case series from community-based practices. These results inform the planned randomized, controlled study of MTX vs placebo with pegloticase to validate the findings observed here.

ACKNOWLEDGMENT

We acknowledge the following employees of Horizon Therapeutics: Lisa Padnick-Silver, PhD and Megan Francis-Sedlak, PhD, for writing and editorial assistance; and Lin Zhao, PhD, and Colleen Canavan, MS, for trial support.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES


