Full Title of Manuscript: Pegloticase in combination with methotrexate in patients with uncontrolled gout: A multicenter, open-label study (MIRROR)

Authors:

John K. Botson, MD, RPh, Orthopedic Physicians Alaska, Anchorage, AK, jbotson@opaak.com

John R.P. Tesser, MD, Arizona Arthritis & Rheumatology Associates, P.C., Phoenix, AZ, john.tesser@azarthritis.com

Ralph Bennett, MD, Arizona Arthritis & Rheumatology Associates, P.C., Phoenix, AZ, Ralph.Bennett@azarthritis.com

Howard M. Kenney, MD, Arthritis Northwest, PLLC, Spokane, WA, hkenney@Arthritisnw.com

Paul M. Peloso, MD, MSc, Horizon Therapeutics, Lake Forest, IL, PPeloso@horizontherapeutics.com

Katie Obermeyer, MS, Horizon Therapeutics, Lake Forest, IL, KObermeyer@horizontherapeutics.com

Brian LaMoreaux, MD, MS, Horizon Therapeutics, Lake Forest, IL, BLaMoreaux@horizontherapeutics.com

Michael E. Weinblatt, MD, Brigham and Women's Hospital, Boston, MA, mweinblatt@bwh.harvard.edu

Jeff Peterson, MD, Western Washington Arthritis Clinic, Bothell, WA, jeff.peterson@wwmedgroup.com

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Corresponding Author:

John K. Botson, MD, RPh

Orthopedic Physicians Alaska

3801 Lake Otis Parkway

Anchorage, AK 99508

jbotson@opaak.com

Short Running Head: Pegloticase response with methotrexate

ABSTRACT

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

Methods: A multicenter, open-label, efficacy and safety study of pegloticase with methotrexate co-treatment was conducted in patients with uncontrolled gout. Patients were administered oral methotrexate (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 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 discontinuing after meeting protocol-defined treatment discontinuation rules (pre-infusion sUA values greater than 6 mg/dL at 2 consecutive scheduled visits). All patients tolerated methotrexate. 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 methotrexate and pegloticase when compared to the previously reported 42% using pegloticase alone. These results support the need for a randomized study of methotrexate or placebo with pegloticase to validate these open label findings.

INTRODUCTION

Gout affects an estimated 9.2 million people (3.9% of adults) in the USA[1] 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 impact soft tissues[4] and other organs, as evidenced by associations between hyperuricemia and hypertension,[5, 6] cardiovascular disease,[7-11] diabetes,[5, 12] kidney disease,[13, 14] and death.[11, 15, 16] The American College of Rheumatology 2020[17] and the European League Against Rheumatism[18] guidelines recommend maintaining sUA levels below 6 mg/dL. Unfortunately, urate-lowering therapies (ULTs) are often under-utilized[19] and a small subset of gout patients cannot tolerate or do not respond.[19] Consequentially, sUA levels remain over 6 mg/dL and urate deposition continues,[20] with an estimated 10% of patients developing chronic tophaceous 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 an FDA-approved medication 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 anti-drug antibodies (ADAs) that accelerate pegloticase clearance.[25-27] Because treatment options for patients with uncontrolled gout are limited, some physicians have co-administered 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 biologicals.[28, 29] Case reports support the successful use of immunomodulators (methotrexate, azathioprine, leflunomide, and cyclosporine) with pegloticase.[27, 30-37] However, these studies are limited and examined different immunomodulatory agents

with varying doses, schedules, and routes. In current methotrexate/pegloticase case series, the proportion of responders (based on each study's definition) was 100% (10/10 patients),[33] 100% (7/7 patients),[30, 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 methotrexate, the current study prospectively examined the efficacy and safety of pegloticase-methotrexate co-therapy in subjects with uncontrolled gout.

MATERIALS AND METHODS

This multi-center, open-label, efficacy and safety study (ClinicalTrials.gov: NCT03635957) was conducted at 6 sites in the USA. The trial was reviewed and approved for all sites by the Western Institutional Review Board (Puyallup, WA; approval number 20182156). All subjects provided written informed consent to participate in the trial and all study conduct adhered to the tenants of 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 (pegloticase and methotrexate) and at least one of the following: inability to maintain sUA <6 mg/dL on other ULT, intolerance to current ULT, or functionally limiting tophaceous deposits (detected clinically or with DECT). Patients were excluded from participation if any of the following were true/present: serious acute bacterial infection (<2 weeks prior), severe chronic/recurrent bacterial infection, immunocompromised status, glucose-6-phosphate dehydrogenase (G6PD) deficiency (tested at Screening), severe chronic renal impairment (GFR <25 mL/min/1.73m^2 or currently on dialysis), or current liver disease (ALT or AST >3 times upper limit). See **Supplemental Table 1** for the complete list of inclusion and exclusion criteria.

Study medications

All patients were to receive methotrexate and pegloticase. A study design schematic is shown in **Figure 1**. Briefly, subjects were screened for eligibility prior to beginning the 4-week methotrexate run-in period

(Week -4 through Day 1), during which subjects received 15 mg/week of oral methotrexate and 1 mg/day oral folic acid. The methotrexate dose was chosen based on several factors. First, a trial examining methotrexate/adalimumab combination therapy for rheumatoid arthritis found that a dose of at least 10 mg/week as 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 methotrexate 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 CIRT trial were reassuring with respect to a methotrexate dose of 15-20 mg/week in a population with similar comorbidities.[40]

During the treatment period (maximum 52 weeks), patients continued weekly methotrexate and daily folic acid and initiated pegloticase treatment (8 mg intravenous pegloticase every 2 weeks). Starting ≥1 week prior to Day 1, all patients were required to start gout flare prophylaxis regimen: colchicine and/or non-steroidal anti-inflammatory 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 (non-tophaceous 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 (1000 mg) the morning of, and intravenous glucocorticoid (200 mg hydrocortisone or 125 mg methylprednisolone over 10-30 min) immediately prior to pegloticase infusion.

Pegloticase uric acid monitoring protocol[24] was followed to minimize the occurrence of IRs. Briefly, patients who had an sUA level >6 mg/dL at two consecutive study visits after Week 2 discontinued therapy.

Study procedures

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, hematology and clinical chemistry panels.

Methotrexate run-in period

Patients initiated methotrexate within 2 weeks of Screening. Immediately prior to methotrexate initiation (-4 weeks), patients underwent study eligibility re-assessment, 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/methotrexate treatment period

All patients were to receive treatment with both pegloticase and methotrexate from day 1 through the end of the treatment 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 **Supplemental Table 2.** 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 event, 2=moderate event, 3=severe event, 4=life-threatening).[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 flare, was pain in joints different than normal? If yes to flare, was pain at rest greater than a 3 out of 10 (0=no pain, 10=worst pain imaginable)? If yes to flare, had joint swelling had occurred?[43]

Data analyses

Study endpoints

The primary endpoint was the proportion of pegloticase responders during Month 6 (Weeks 20, 22, and 24). Patients were considered 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 during Month 3 (Weeks 10, 12, and 14) and overall (during Months 3 and 6 combined). The proportion of patients who had an sUA of <5 mg/dL during Month 3, Month 6, and overall for at least 80% of the time was also examined. A patient was declared a non-responder if they met protocol-defined treatment discontinuation rules or had missing sUA values at all planned evaluation time points during Month 3 or 6. The mean change in sUA from baseline was examined at Weeks 14 and 24. The change from baseline analysis was performed on observed data, with no imputation for missing data.

Safety and tolerability were examined using incidences of IRs, anaphylaxis, gout flare, cardiovascular events, and AEs.

Statistical methods

A sample size of 12-16 subjects was planned for this study. An exact test for proportions with a 5% type I error demonstrated that the primary efficacy endpoint would be statistically greater than 43.5% (proportion of responders during Month 6 in the phase 3 studies) if at least 10/13 subjects (77%) were responders. In that case, the lower bound of the 95% confidence interval (95% CI) for the proportion of responders would be 46%.

This report describes the results of an analysis conducted after all enrolled subjects had been followed through Week 24. The primary and secondary endpoints are presented along with the 24-week safety findings. All efficacy and safety analyses were performed using the modified intention-to-treat (mITT) population, defined as all subjects who received at least 1 dose of pegloticase. Safety analyses were

also performed using the ITT population, defined as all patients who received at least one dose of methotrexate, on data collected during the methotrexate run-in period.

RESULTS

A total of 17 patients were screened for study inclusion between September 26, 2018 and April 2, 2019, with 15 patients starting methotrexate treatment. Fourteen patients completed the methotrexate run-in period. One patient began methotrexate 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 received at least 1 dose of pegloticase and constituted the mITT population. Eleven patients completed 24 weeks of pegloticase + methotrexate treatment.

In the mITT population, all patients were male with an average age of 49.3 ± 8.7 years. Most patients were white and had visible tophi at the time of enrollment (**Table 1**). Mean baseline sUA value obtained prior to the first pegloticase infusion was 9.2 ± 2.5 mg/dL. Mean eGFR at Week -4 in the mITT population was 84.6 ± 21.7 ml/min/1.73m^2 (range: 44-126). Six patients had an eGFR ≥90 ml/min/1.73m^2, 6 patients had CKD stage 2, 1 had CKD stage 3a and 1 CKD stage 3b.

Patients were administered a mean total methotrexate dosage of 64.4 ± 7.7 mg (range: 60-75) during the methotrexate 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 + methotrexate treatment and 11 patients (78.6%) completed all 12 scheduled pegloticase infusions. During this treatment period, the mean weekly dose of methotrexate 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 one patient discontinuing after 2 infusions and one 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 remained at 78.6% for all three 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/methotrexate co-therapy, the 14 patients had 6.4 ± 7.9 joints affected by tophi (median: 4.0, range: 0 to 31), and the mean number of joints affected by tophi at their last assessment was 2.6 ± 3.5 (median: 1, range: 0 to 12).

Safety

Ten of 15 patients (66.7%) in the ITT population who were administered methotrexate during the run-in period experienced one 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 one or more AEs. A complete listing of AEs can be found in **Table 3**, but 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, gout flare, and cardiovascular events (**Table 4**). An IR in one 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 two 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 two severe flares (grade 3), all were mild-to-moderate in intensity (grade 1-2, Rheumatology Common Toxicity Criteria v.2.0[42]). 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, 5 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 cardiovascular event (MACE, includes non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and congestive heart failure) and no deaths occurred. One case of bacterial sepsis secondary to cholecystitis (Investigator deemed unrelated to trial medications) occurred and was classified as a serious AE.

In the run-in period, there was an initial relatively minor and not unexpected increase in LFTs followed by stabilization (**Figure 2B**). Prior to the first methotrexate 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 post-baseline.

Two patients had a methotrexate dose reduction during the co-treatment period. One was inadvertent (took 12.5 instead of 15 mg on two occasions). One patient had a reduction to 10 mg/week in response to AEs (leukopenia [2.5 x 10^9/L], neutropenia [1.0 x 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 eGFR of 61 at screening, 76 at the start of MTX, and 58 ml/min/1.73m^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] Methotrexate 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 antirheumatic 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.[29, 45, 46]

Pegloticase has well-established efficacy, but duration of response is limited in some patients due to the development of ADAs which primarily bind to the molecule's polyethylene glycol components.[23, 26] 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.[24, 25] Since immunomodulating therapies are not part of standard gout care, unlike other biologics, pegloticase has historically been used as monotherapy.[47]

In an effort to help more uncontrolled gout patients complete a full course of therapy, some clinicians have administered immunomodulation co-treatment with pegloticase. The most studied agent has been methotrexate, but azathioprine, leflunomide, and cyclosporine have also shown improved pegloticase response rates[30, 33-37] compared to the 42% observed in phase 3 clinical trials.[23] Botson and Peterson[33] showed a 100% response rate in 10 patients co-treated with oral methotrexate, Albert et al[35] showed an 80% response rate in 10 patients co-treated with oral or subcutaneous methotrexate, and Bessen et al[30, 34] showed a 100% response rate in 7 patients co-treated with methotrexate. Two additional cases reported successful pegloticase therapy with other immunomodulators (1 case of azathioprine

use,[34] 1 case of chronic mycophenolate mofetil and cyclosporine use in a heart transplant patient[31]), highlighting the potential of immunomodulation to increase the pegloticase responder rate.

This prospective, open-label clinical trial sought to evaluate the ability of methotrexate given concomitantly with pegloticase to enhance the response rate seen with pegloticase alone. All included patients were treated with oral methotrexate 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 3 trials.[23] 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 three months of treatment. One serious AE of bacterial sepsis occurred; it resolved and the site investigator determined it was unrelated to study drug. Other AEs occurring >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 methotrexate co-administered 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 methotrexate 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 methotrexate 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

3 program without methotrexate, 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 methotrexate 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 methotrexate vs pegloticase plus placebo in a controlled trial. Such a trial would also confirm that the responder rate increase resulted from methotrexate use and that these finding were not confounded by other factors, including differences in steroid prophylactic agents (methylprednisolone vs. hydrocortisone[48]). Therefore, a randomized, double-blind, placebo-controlled (pegloticase with placebo), efficacy and safety study is currently ongoing (MIRROR RCT, 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 which 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 methotrexate versus placebo with pegloticase to validate the findings observed here.

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Table 1. Baseline Characteristics for the Modified Intent-to-Treat (mITT) Population

	mITT Population N=14
Age, mean (SD), years	49.3 (8.66)
Male sex, n (%)	14 (100)
Race, n (%)	
White	11 (78.6)
Black	0 (0)
Asian	2 (14.3)
Native Hawaiian or other Pacific Islander	0 (0)
Other	1 (7.1)
Body mass index (BMI), mean (SD), kg/m^2	33.9 (7.0)
Estimated glomerular filtration rate (eGFR), mean (SD), ml/min/1.73 m^2	84.6 (21.65)
Gout characteristics	
Time since first gout diagnosis, mean (SD), years	13.8 (7.4)
Number of gout flares in the 12 months prior to screening, mean (SD)	10.8 (8.5)
History of tophi, n (%)	12 (85.7)
Baseline serum uric acid, mean (SD), mg/dL	9.2 (2.5)
Smoking status, n (%)	
Never	4 (28.6)
Current	5 (35.7)
Former	5 (35.7)

Table 2. Primary and Secondary Endpoints

Efficacy Endpoint	**mITT Population**
	N=14
Number of patients who maintained sUA <6 mg/dL for at least 80% of the time during:	
Month 3, n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
****Month 6**, n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
Months 3 and 6 (Overall), n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
Number of patients who maintained sUA <5 mg/dL for at least 80% of the time during:	
Month 3, n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
Month 6, n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
Months 3 and 6 (Overall), n (%) [95% CI]	**11 (78.6) [49.2, 95.3]**
sUA change from baseline to Week 14 (mg/dL)	**n=11**
Mean (SD)	**-9.0 (2.8)**
Median	**-8.8**
Min, Max	**-15.5, -4.4**
sUA change from baseline to Week 24 (mg/dL)	**n=11**
Mean (SD)	**-9.0 (2.8)**
Median	**-8.8**
Min, Max	**-15.5, -4.4**

****Primary endpoint**

Note: Confidence intervals (CI) based on exact (Clopper-Pearson) CI

Table 3. Adverse Events Observed During the Methotrexate Run-In and Pegloticase + Methotrexate Treatment Periods

	Methotrexate Run-In Period ITT Population N=15 *no. of patients (%)*	**Pegloticase + Methotrexate Period mITT Population N=14** *no. of patients (%)*
Any adverse event	**10 (66.7)**	**14 (100)**
Any serious adverse event	**0**	**1 (7.1)**
Adverse events occurring in >1 patient in either period		
Gout flare	**5 (33.3)**	**12 (85.7)**
Diarrhea	**1 (6.7)**	**3 (21.4)**
Upper respiratory tract infection	**0**	**3 (21.4)**
Sinusitis	**0**	**2 (14.3)**
Muscle strain	**0**	**2 (14.3)**
Hypertension	**0**	**2 (14.3)**
Nausea	**2 (13.3)**	**0**
Abdominal discomfort	**2 (13.3)**	**0**

ITT, intent to treat (any patient exposed to methotrexate during the run-in Period); mITT, modified intent-to-treat (any patient exposed to pegloticase during the pegloticase + methotrexate treatment period).

Table 4. Safety Endpoints

Adverse Events of Special Interest	Pegloticase + Methotrexate Period mITT Population
Infusion reactions, No. patients/No. treated (%)	1 /14 (7.1) †
Anaphylaxis, No. patients/No. treated (%)	0/14 (0)
Cardiovascular events*, No. patients/No. treated (%)	0/14 (0)
Subjects experiencing gout flare, No. patients/No. treated (%)	12/14 (85.7)
Among patients with ≥1 flare	
Mean number of flares (SD)	5.6 (4.0)
Median	5
Min, Max	1, 15
Day 1 to Week 12	
Subjects experiencing gout flares, No. patients/No. treated (%)	12/14 (85.7)
Among patients with ≥1 flare	
Mean number of flares (SD)	4.3 (2.2)
Median	4
Min, Max	1, 8
Week 12 to Week 24	
Subjects experiencing gout flare, No. patients/No. treated (%)*	5/11 (45.5)
Among patients with ≥1 flare	
Mean number of flares (SD)	3.0 (2.6)

Median	**2**
Min, Max	**1, 7**

***11 subjects remained on pegloticase + methotrexate therapy during week 12 to week 24.**

†The investigator reported infusion reaction was a mild cough, occurring during the 5th infusion and lasting for 1 hour, not accompanied by other signs and symptoms and not requiring specific intervention.

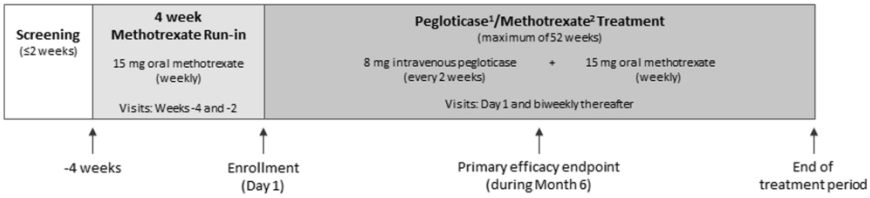

Figure 1. Study schema showing the screening, run-in, and pegloticase/methotrexate co-treatment periods.
1. Protocol-defined treatment discontinuation rules applied (discontinue therapy if two consecutive sUA >6 mg/dL beginning at Week 2).
2. Key efficacy assessments conducted during Months 3 (Weeks 10-14) and 6 (Weeks 20-24).

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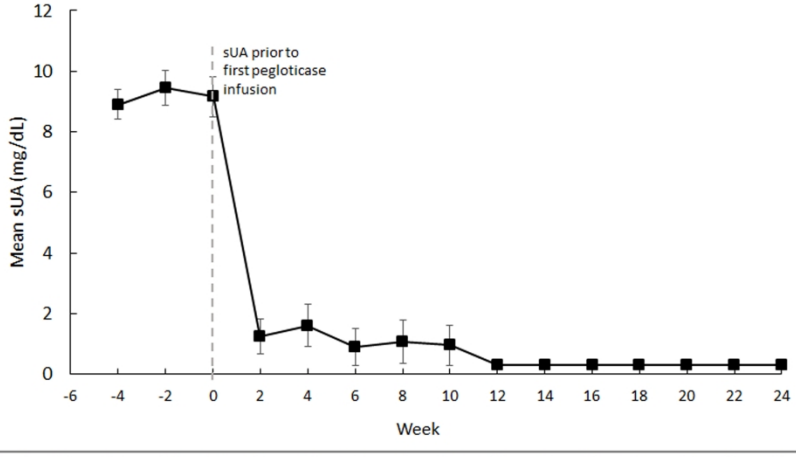
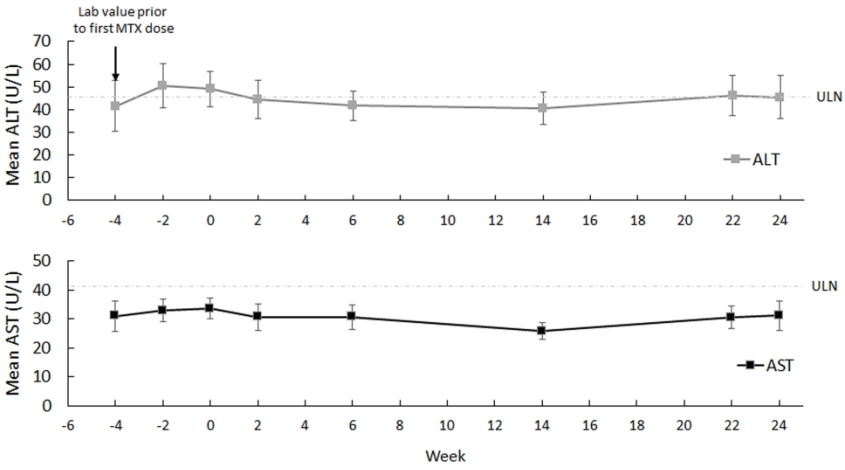
A.



Number of subjects	14	14	14	14	14	13	12	12	11	11	11	11	11	11	11

B.



Number of subjects	14	14	14	14	14	11	11	11
Number with ALT ≥ULN	3	5	6	4	5	5	5	5
Number with AST ≥ULN	2	4	3	2	3	1	3	2

Figure 2A. Pre-Infusion Serum Uric Acid Levels During Pegloticase + Methotrexate Treatment Period, 2B. Liver Function Test Results Through Week 24
Error bars represent standard error.