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Reducing Immunogenicity of Pegloticase (RECIPE) with Concomitant Use of Mycophenolate Mofetil in Patients with Refractory Gout— a Phase II Double Blind Placebo Controlled Randomized Trial

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ABSTRACT

Objectives: Pegloticase is used for treatment of severe gout patients but its use is limited by immunogenicity. We evaluated whether mycophenolate mofetil (MMF) would prolong the efficacy of pegloticase.

Methods: Participants were randomized 3:1 to 1000 mg MMF twice daily or placebo (PBO) for 14 weeks starting 2 weeks before and while receiving intravenous pegloticase 8 mg biweekly for 24 weeks. The primary endpoint was proportion of patients who sustained a serum urate (SU) level of ≤ 6 mg/dl at 12 weeks. Secondary endpoints included 24-week durability of SU ≤ 6 mg/dl and rate of adverse events (AEs). Fisher's exact test and Wilcoxon two-sample test were used for analyses along with Kaplan-Meier estimates and log-rank tests.

Results: 32 participants received at least one dose of pegloticase. Participants were predominantly men (88%), with mean age 55.2 years, gout duration of 13.4 years, and mean baseline SU of 9.2 mg/dL. At 12 weeks, 19 of 22 (86%) in the MMF arm achieved SU ≤ 6 mg/dl compared to 4 of 10 (40%) in PBO arm (p-value = 0.01). At week 24, the SU was ≤ 6 mg/dl in 68% of MMF arm vs. 30% in PBO (p-value = 0.06), and rates of AEs were similar between groups with the PBO arm having more infusion reactions (30% vs. 0%).

Conclusion: MMF therapy with pegloticase was well tolerated and showed a clinically meaningful improvement in targeted SU ≤6 mg/dL at 12 and 24 weeks. This study suggests an innovative approach to pegloticase therapy in gout.

INTRODUCTION

Gout is a common chronic inflammatory arthritis associated with acute flares and when left untreated results in chronic and potentially destructive arthritis and tophi formation. Pegloticase is a recombinant, pegylated uricase, approved in the US for the treatment of patients with gout who fail conventional oral urate-lowering therapy (ULT).[1] Despite its remarkable efficacy as "debulking therapy" in people with severe gout,[2] its potent immunogenic response leads to

clearing anti-drug antibodies and higher rates of infusion reaction (IR) and limits clinical response.[3,4] A relationship between the loss of urate-lowering efficacy of pegloticase, indicated by a rise in SU levels, and high-titer antibody formation was noted in post-hoc analyses of two pivotal studies.[1,5] Participants with high anti-pegloticase antibody titers experienced a significant loss of pegloticase activity that is attributed to faster drug clearance in the presence of these antibodies. Sixty-nine (41%) of 169 patients receiving pegloticase developed high titer anti-pegloticase antibodies and subsequently lost response to the drug.[6] In addition, 60% participants with high titers developed an IR.[1,7] Based in part on the ability of immunomodulatory drugs such as methotrexate to attenuate anti-drug antibodies when using certain biologics, the co-administration of such agents could disrupt the ability of pegloticase to induce production of anti-pegloticase antibodies, thus mitigating the loss of efficacy.[6-9] Indeed, recently published case series suggest that methotrexate, azathioprine and leflunomide may attenuate pegloticase induced anti-drug antibody formation production.[10-13] Through inhibition of T and B cell proliferation,[14,15] mycophenolate mofetil (MMF) is another immune modulating drug commonly and successfully used in other rheumatic diseases, with an established safety profile in patients with chronic kidney disease (CKD) which is a frequent co-morbidity among uncontrolled gout patients. [16-19] We tested the feasibility of using a short-term course of MMF started prior to initiation of pegloticase and continued though the first twelve weeks of combined therapy to increase the proportion of patients who were able to achieve a sustained reduction in serum urate level during the course of pegloticase therapy¸ thus improving the efficacy and safety of pegloticase infusions.

PATIENTS AND METHODS

We designed a Phase II proof-of-concept, placebo controlled randomized trial of short term MMF vs. placebo (PBO). Participants from five large practices were randomized in a 3:1 ratio by site to either MMF + pegloticase (MMF+Peg) or PBO + pegloticase (PBO+Peg) initiated 2 weeks before the administration of pegloticase at the FDA approved dose of 8 mg administered intravenously every 2 weeks for a total of 12 infusions. Based on an informal survey of 15 rheumatologists who preferred MMF or methotrexate over other drugs, we chose MMF to serve as a potential immunodulator to pegloticase in a proof-of-concept Phase II trial. MMF or placebo were continued for the first 12 weeks of the 24-week duration of pegloticase therapy. All participants then received pegloticase alone for the remaining 12 weeks. The rationale for choosing the primary end point at 12 weeks were: 1) historical cohort data demonstrating development of antibodies in the first 6 weeks of pegloticase use,[11] 2) concerns about the possible safety of concomitant use of MMF with Pegloticase for a longer duration, and 3) interest in determining if the durability of response changed with stopping MMF after 12 weeks.

The trial was approved by the IRB at each participating research center and each patient signed the IRB approved consent form. We received the Investigational New Drug approval from the FDA on 11/29/2017 and the study was registered on the clinicaltrials.gov (NCT NCT03303989) on 09/29/2017. The study inclusion criteria for eligibility were: a)

adults > 18 years of age, b) gout based on 2015 ACR/ EULAR gout criteria,[20,21] c) chronic refractory gout defined as persons whose signs and symptoms are inadequately controlled with ULT (e.g., xanthine oxidase inhibitors or uricosuric agents) at a medically appropriate dose or for whom these drugs are contraindicated, d) hyperuricemia (i.e., SU > 6 mg/dL) at the screening visit, and e) never received pegloticase or other uricase therapies. Exclusion criteria were weight > 160 kg (352.74 lbs.), infection in the prior 2 weeks, and an immunocompromised status.

Study visits and drug administration: Study visits included a screening visit to confirm study eligibility, explain procedures, and allow participants to engage in the informed consent process. Following the screening visit participants were randomized and begin a PBO or MMF run-in at 500 mg/twice per day for 7 days, and if tolerated the dose was titrated up to 1000mg/twice per day for an additional 7 days prior to the initial pegloticase infusion. Participants who were not able to tolerate the PBO or MMF dose due to gastrointestinal or other AEs during the run-in period were withdrawn from the study and not followed further. All participants received gout flare prophylaxis (colchicine 0.6 mg/day or low dose nonsteroidal anti-inflammatory medication) starting 7 days prior to first pegloticase infusion. On the day of each of the pegloticase infusions, consistent with standard of care for pegloticase administration, all participants received pre-infusion prophylaxis (i.e., oral fexofenadine (60 mg, oral) the night before; fexofenadine (60 mg, oral) and acetaminophen (1000 mg, oral) the morning of the infusion; and hydrocortisone (200 mg, IV) immediately prior to the infusion). If an IR occurred or there were two consecutive levels of SU > 6 mg/dL prior to the pegloticase infusion, pegloticase infusions were discontinued and the participant was considered a non-responder and was followed off pegloticase for the full study visits as scheduled.

It was expected that many participants would continue to have gout flares during the study, since gout flares typically occur early in the course of pegloticase treatment.[22] Colchicine, 0.6 mg up to a maximum of 3 times per day[23,24] for 1 week was the preferred therapy to manage acute flares, at the discretion of managing physician/investigator. An alternative or additional treatment was a 7-day course of glucocorticoids or use of nonsteroidal anti-inflammatory drugs. Adequate pain control was maintained by the study physicians, who also served as the managing physicians for all gout care of study participants.

Outcomes: The primary clinical endpoints were: a) the proportion of participants achieving and maintaining a serum urate (SU) ≤ to 6 mg/dL over 12 weeks in the MMF+Peg group vs. PBO+Peg group, and b) incidence and types of AE/IR during the study. The secondary clinical endpoints were: 1) 6-month durability of immune modulation after discontinuation of the short course of MMF by a) absolute change in serum urate from baseline to Week 24, and Week 12 to Week 24, and b) proportion of participants with serum urate ≤ 6 mg/dL through 24 weeks, and Week 12 to Week 24; and 2) patient reported outcomes (PROs) using the National institute of Health (NIH) supported Patient Reported Outcomes Measurement Information System® (PROMIS)[25,26] and Gout Impact Scale (GIS)[27,28]instruments. AEs were collected and summarized based on severity and organ systems.

Randomization: Participants were randomized in a 3:1 ratio to either MMF+Peg or to PBO+Peg. Randomization allocation was balanced over time and by site using a double-blind design. Treatment assignment was determined by a random number generator and stratified by site using a central randomization system to ensure proper allocation. Subjects who dropped out during the run-in period (before they received pegloticase) would not provide scientifically meaningful data were not counted in the required sample size and thus they were replaced.

Data Analyses: Descriptive analyses (means, standard deviations (SD), medians, interquartile ranges (IQR) and frequency distributions (%) were conducted to describe the study subjects. Fisher's exact tests and Wilcoxon two-sample tests were performed to compare baseline and clinical characteristics between treatment groups as appropriate. Efficacy of MMF was examined by the proportion of responders in MMF+Peg compared to PBO+Peg. Rates of the primary outcome were compared using proportions and 95% confidence intervals and tested for differences using Fisher's exact test. To quantify the efficacy of MMF, Kaplan-Meier estimates and a log-rank test were performed to compare survival curves between groups. Adverse events across groups were summarized using frequency and percentages. Continuous secondary outcome variables were summarized using means with standard deviation (SD), and/or median and interquartile ranges (IQR) with 95% confidence intervals and compared by groups using t-tests or Wilcoxon tests as appropriate. All hypothesis tests were two-tailed and a p-value ($p < 0.05$) indicated statistical significance. Analyses were conducted using SAS (Cary, NC) Version 9.4.

Sample Size: The study was designed assuming the historical responder status (i.e., success rate) for pegloticase of 40%.[6] The goal of this proof-of-concept study was to reduce the expected 60% failure rate by at least half. Therefore, we hypothesized that MMF+Peg would yield a success rate of at least 70% (at week 12). A decision matrix based on the differences in failures between MMF+Peg and PBO+Peg was constructed using Fisher's exact test. This decision matrix to pursue a subsequent study represented the area that achieves a significant (2 tailed $p<0.10$) Fisher's exact test that MMF+Peg is better than PBO+Peg. In this proof-of-principle study, we calculated that we needed to have a minimum of 20 informative participants on MMF+Peg therapy (i.e., participants who achieve either pegloticase responder or non-responder status (our primary endpoint)).

RESULTS

Five sites in the U.S. screened 42 participants with uncontrolled gout who met the inclusion and exclusion criteria between May 2018 to October 2019. **Figure 1** (Study consort) provides details on the 35 participants who were randomized. Three participants withdrew after randomization, but prior to first pegloticase infusion and were not counted in the required sample size; 32 participants received at least one dose of pegloticase and were included in modified intention-to-treat analyses. Baseline characteristics of the 32 participants (22 in MMF+Peg, 10 in PBO+Peg) were similar across the two treatment arms – MMF+Peg and PBO+Peg including gout flares, severity of disease and oral

ULT (Table 1). At screening, the majority of participants were on optimized ULT (59% were on allopurinol and 16% were on febuxostat); 63% of participants reported > 1 flare in the past year. Participants at baseline were predominantly men (88%), Caucasian (78%) with a mean age of 55.2 years (SD=9.7). Mean duration of gout was 13.4 years (SD=9.0), mean SU was 9.2 mg/dL (SD=1.6). Tophi were present in 88% of participants with a mean ACR/EULAR Gout Criteria score of 13.7 (SD=2.8) indicating a high burden of gout. At baseline both arms had similar comorbidities – hypertension (82% vs 70%), diabetes mellitus/metabolic syndrome (14% vs 20%), coronary artery disease/peripheral vascular disease (41% vs.70%), BMI>30 (86% vs. 90%) and renal insufficiency (defined as eGFR < 90 mL/min; 73% vs. 70%).

Primary Outcomes: At week 12, 19 of 22 (86%) in the MMF+Peg arm achieved the primary outcome (SU ≤ 6mg/dL), compared to 4 of 10 (40%) in placebo, p-value=0.01. Figure 2 demonstrates that the proportion of subjects maintaining a SU < 6 mg/dL at 12 weeks was significantly greater (p=0.02) in the MMF+Peg arm. In our post hoc analysis, we examined a different cut point for SU of <5 mg/dl as 12 week period, there was a significant difference between treatment arms in the primary endpoint at week 12 (86%. MMF+Peg group vs. 30% PBO + pegloticase group, p< 0.05; data not shown in a tabular format). A total of 54 AEs were reported by 22 participants during the study period, with estimated rates of AEs generally similar between groups, not accounting for exposure time. (**Table 3**). The most commonly reported AEs were musculoskeletal (41% vs 10%) which included arthralgia, myalgia, low back pain, orthopedic trauma, bursitis tendonitis, and muscle cramps (not accounting for exposure time). Following musculoskeletal disorders, gastrointestinal disorders (18% vs 10%), respiratory issues, (18% vs. 0%), infections (9% vs. 0%), and other (e.g., abnormal blood tests, anxiety, fatigue; 41% vs 50%) were the most common. Four patients (3 in the MMF+Peg) were found to have a transient elevation in transaminases and 1 patient in the PBO+Peg showed a reversible decline in their hemoglobin and hematocrit. Rates of AEs per month was similar between groups – MMF+Peg (0.3) and PBO+Peg (0.4). Infusion reactions (IRs) occurred in 3 participants in the placebo arm (30%) compared to none in the MMF+Peg arm. Two participants experienced IRs during their first infusion and the third during the second infusion. One IR was classified as serious and involved hospitalization. All IRs resolved, and no deaths occurred. A total of 4 serious adverse events (SAEs) occurred in 3 participants during the study period. This included the one serious IR in the PBO+Peg arm, and three SAEs in the MMF+Peg arm that were unrelated (e.g., motor vehicle crash) or possibly related to the study (e.g., chest pain, abdominal pain). All SAEs resolved, and no deaths or other unanticipated problems were reported in either arm.

Secondary Outcomes: At week 24, SU response (≤6 mg/dL) was sustained in 68% of MMF+Peg arm vs. 30% in the PBO+Peg arm (p=0.06; Table 2). We found no significant differences between groups in absolute change in SU from baseline to Week 24, and Week 12 to Week 24. Gout flares occurred in both treatment groups throughout the study period. **Figure 3** details the incidence of gout flares (proportion of patients suffering at least 1 flare) in the MMF+Peg arm compared to the PBO+Peg arm. The proportion of patients in the MMF+Peg arm (and for whom data were available

at that particular time point) who reported flares was significantly reduced from baseline (45%) to 24 weeks (21%) (p=0.02) and from 12 weeks (63%) to 24 (21%) weeks (p=0.01). We found no significant temporal changes among the small group of patients who continued on pegloticase in the PBO+Peg arm. We observed no significant differences between groups comparing the proportion of gout flares within the MMF+Peg and PBO+Peg arms at baseline, week 12, and week 24. Finally, we found no differences between treatment arms in the patient reported pain intensity or physical function using the PROMIS instruments, and no group difference was seen in the gout-specific patient reported GIS scales (Table 2).

DISCUSSION

Use of pegloticase is limited by the incidence of infusion reactions, and loss of efficacy which is attributed to production of antibodies to pegloticase. Thus, modulating this antibody response with MMF as an immunomodulatory drug was appealing based on prior evidence suggesting MMF could reduce antidrug antibodies.[11,29,30] We found that short-term concomitant use of MMF with pegloticase was associated with a statistically significant and clinically meaningful improvement on the proportion of participants achieving and maintaining a SU below our target and was generally well tolerated and without infusion reactions. Our primary endpoint of an SU response of ≤6 mg/dL, and SU ≤6 mg/dL was sustained in nearly 70 percent of participants in the MMF+Peg through 24 weeks indicating the potential for longer-term efficacy of this approach. This result suggests that longer duration of immunosuppression would be valuable to evaluate in future trials. We found no differences in the patient reported outcome measures, most likely related to our study design that required subjects who met SU related stopping criteria to discontinue from the trial. Significantly more patients in the PBO+Peg arm discontinued potentially due to anti-PEG antibody production. In addition, a greater proportion of individuals in the MMF+Peg arm continued to experiences gout flares. An increase in the incidence of gout flares over 24 weeks was not surprising, since it is well known that gout flares increase during initiation of pegloticase, in part due to the profound lowering of urate level with pegloticase leading to mobilization of latent urate deposits.. [31]

Recent case series or uncontrolled observational studies with different immunomodulatory agents have suggested the potential to improve the durability of the response to pegloticase infusions, but to our knowledge, our study is the first randomized controlled trial to demonstrate this effect. In one small study, ten patients received pegloticase biweekly along with oral MTX 15 mg weekly and >80% of pre-infusion SU levels were ≤6.0 mg/dL, with no associated infusion reactions.[32] A second study from a single community rheumatology practice also included a series of 10 patients who received subcutaneous MTX with a similar 80% response rate, no safety concerns and one mild infusion reaction.[33] Finally, the open-label MIRROR trial found similar results, with 11 of14 patients receiving pegloticase biweekly along with oral MTX responding.[34] A case series of 10 patients showed 70% achieved a complete response when co-treated with pegloticase and leflunomide. Finally, azathioprine was studied in combination with pegloticase and preliminary results from an open-label trial of 12 patients demonstrated 60% achieved a complete response without adverse events;

two patients were still receiving treatment with persistent urate-lowering therapy.[35] These encouraging but inconclusive case series and some encouraging data from open label trials led us to design a double blind PBO controlled randomized trial, which provides the advantage of minimizing bias and confounding factors seen in observational studies and allowing possible causal inference through the use of a contemporaneous control group.

While there is likely not one optimal immunomodulatory agent for use with pegloticase, MMF has strengths and limitations compared with other possible agents. Azathioprine metabolism is dependent on the thiopurine methyl transferase pathway, whereas MMF does not potentiate toxicity with concomitant use of allopurinol (which can be inadvertently administered even in patients receiving pegloticase)[36-3839] Importantly, azathioprine is often less well tolerated than MMF, and requires greater dose titration.[29,30,40,41] Also in contrast to MMF, methotrexate requires a longer run-in time and gradual dose titration to induce clinically meaningful suppression of T and B cells.[42] MTX may be problematic in patients with severe gout and multiple comorbidities (e.g., chronic kidney disease), who may be commonly drinking alcoholic beverages, or who demonstrate more frequent steatohepatitis; thus placing them at higher risk of side effects (e.g., folate deficiency anemia and liver dysfunction).[43,44] With MTX, and also with leflunomide, there is potential impact on liver/kidney toxicity and the possible confounding benefit of lowering SU and suppressing gouty attacks, effects previously reported with both agents.[44-46] MMF is commonly used by rheumatologists for systemic lupus erythematosus, systemic sclerosis, and other connective tissue diseases. MMF has potential gastrointestinal intolerance, and in rare cases hepato-renal and/or hematologic toxicity.[47-49] Of note, we did not observe such findings in our study, although we were significantly underpowered to detect such safety signals in this study.

While our study has strengths in its design (i.e., double-blind, randomized, placebo-controlled design) and our success rate in the control arm was similar to the past phase 3 results suggesting some generalizability, there are limitations of our study as well.[1,5,6,9] A limitation of the study was the small sample size as it was designed primarily to evaluate feasibility of concomitant MMF with pegloticase therapy. Our intent was to randomize participants in a 3:1 ratio to active drug versus placebo. Given the small size of the trial and the varied recruitment by site we did not fully achieve that goal, however the objective of unbiased assignment was maintained (see supplemental Table 1). Larger studies are needed to better assess the long-term safety profile of MMF immunomodulation with pegloticase.

In summary, our proof-of-concept study tested the principle that a short-term course of MMF can mitigate immunogenicity to pegloticase. To our knowledge, this is the first randomized controlled trial to demonstrate differential prolonged efficacy of pegloticase in the setting of co-administration of an immunomodulatory agent, as well as providing safety information on the combination with MMF which was well tolerated. Furthermore, durability of response to pegloticase and a significant difference between groups at 24 weeks indicates the durability of MMF-induced immunosuppression after MMF discontinuation at 12 weeks. Our study serves as an innovative approach to customize pegloticase therapy in patients with severe gout and potentially ameliorate infusion reactions. The high personal and societal burden of chronic refractory gout mandates intensive gout management. Our clinical trial presents

successful preliminary evidence for future testing of concomitant immune modulating therapy with pegloticase in rigorously conducted investigations.

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Figure 1: Consort Diagram

*Primary Outcome

Table 1. Baseline Demographics and clinical characteristics at baseline of patients in the treatment arms

Gender (%) Men, n (%)	19 (86)	9 (90)	0.99

Age in years, mean (SD)	55.0 (9.4)	55.5 (10.7)	0.91
2015 ACR/EULAR criteria points, mean (SD)	13.5 (2.8)	13.8 (2.7)	0.88
Gout flare history			
Flare within last year, N (%)	15 (68)	5 (50)	0.44
Number of flares last year, median (Q1, Q3)	1 (0, 2)	1 (0, 1)	0.28
Age at diagnosis, years, mean (SD)	40.9 (14.7)	42.1 (12.6)	0.99
Duration of gout, years, mean (SD)	13.3 (9.8)	13.4 (7.4)	0.82
PROMIS items			
Pain intensity T-Score, mean (SD)*	50.8 (11.3)	45.0 (12.4)	0.35
Physical function T-Score, mean (SD)@	37.5 (7.8)	33.8 (6.4)	0.88
Pain score History (0 to 10, 10 being the worst), mean (SD)	4.5 (4.0)	2.8 (3.3)	0.36
Gout impact score at (range: 0-96)			
Mean (SD)	45.7 (7.5)	46.4 (7.1)	0.79
Oral urate lowering medications			
Allopurinol	13 (59)	6 (60)	0.99
Febuxostat	4 (18)	1 (10)	0.99
Acute gout therapy			
Colchicine	9 (41)	5 (50)	0.71
NSAID	16 (73)	5 (50)	0.44
Corticosteroids	4 (18)	2 (20)	0.99
Alcoholic beverages Consumption (number of drinks/day)			
0	11 (50)	3 (30)	0.62
1-2	7 (32)	4 (40)	
>2	4 (18)	3 (30)	
Serum urate level, mg/dL mean (SD)	8.9 (1.8)	9.8 (1.3)	0.15

Serum urate levels, N (%)			
≤ 6 mg/dL	2 (9)	0 (0)	0.9999
> 6 mg/dL	20 (91)	10 (100)	
eGFR (CKD), mean (SD)	81.3 (29.3)	78.2 (18.4)	0.9999
45-59 (mL/min/1,73m^2), N (%)	4 (18)	2 (20)	
60-89 (mL/min/1,73 m^2), N (%)	12 (55)	5 (50)	
> 90 (mL/min/1,73 m^2), N (%)	6 (27)	3 (30)	
Presence of Tophi, N (%)	19 (86)	9 (90)	0.99
BMI N (%)			0.5380
25 to < 30	3 (14)	1 (10)	
30 to < 45	18 (82)	7 (70)	
≥45	1 (4)	2 (20)	
Comorbidities N (%)			
Diabetes Mellitus /Metabolic Syndrome	3 (14)	2 (20)	0.6367
CVA/PVD/Heart Disease	2 (9)	7 (70)	0.0010
Systemic Hypertension	1 (5)	7 (70)	0.0003
Dyslipidemia	18 (82)	4 (40)	0.0369
Kidney Stones	4 (18)	5 (50)	0.0960

*Higher score= more pain intensity; @Lower score= more physical limitations; SD= standard deviation, mL=milliliter; BMI=body mass index, CVA=cerebral vascular disease, eGFR=estimated glomerular filtration rate, PVD=peripheral vascular disease

Table 2. Primary Efficacy Outcome and Secondary Clinical Outcomes

Serum urate ≤ 6 mg/dL up to week 12	86% [65, 97] (19/22)	40% [12, 74] (4/10)	46% [13, 80]	0.01
Serum urate ≤ 6 mg/dL up to week 24	68% [49, 88] (15/22)	30% [2, 58] (3/10)	38% [4, 73]	0.06
Serum urate ≤ 6 mg/dL from week 12 to week 24	79% [54, 94] (15/19)	75% [19, 99] (3/4)	4% [-42, 50]	0.99
Absolute serum urate change up to week 24	7.5 (1.8, 8.9) 5.7 (4.0) (22)	3.1 (1.4, 5.7) 4.2 (4.1) (9)	1.5 [-1.8, 4.7]	0.41
Absolute serum urate change from week 12 to week 24	0.1 (0, 5.2) 1.9 (3.0) (19)	0.05 (0, 0.2) 0.1 (0.1) (4)	1.8 [-1.3, 5.0]	0.48

*PROMIS Pain intensity T-Score Scores at 12 weeks	49.4 (43.5, 57.5) 48.8 (9.2) (19)	49.4 (20.2, 52.1) 47.2 (6.2) (3)	1.5 [-10.1, 13.1]	0.86
*PROMIS Physical function T-Score	34.4 (29.1, 45.3) 37.2 (11.0) (19)	32.1 (29.1, 1.8) 34.3 (6.6) (3)	2.8 [-11.0, 16.7]	0.86
$Pain score History	5.5 (3.0, 8.0) 5.4 (3.0) (10)	4.5 (3.5, 7.5) 5.5 (3.1) (4)	-0.1 [-4.0, 3.8]	0.99
#Revised gout impact score at 12 weeks	44.0 (39.0, 49.0) 43.7 (6.9) (19)	38.0 (37.0, 47.0) 40.7 (5.5) (3)	3.0 [-5.8, 11.8]	0.41

*The higher score the more severity, range; $Scale of 0 to 10, the higher had worst imaginable pain; #The higher score the more severity, range: 0-96;

Table 3. Treatment-related Adverse Events

Any AE	15 (68%)	7 (70%)
Any SAE	2 (9%)	1 (10%)
Discontinuation from treatment due to AE	1 (5%)	3 (30%)
Most Commonly Reported		
Cardiac	2 (9%) [2]	1 (10%) [1]
Gastrointestinal	4 (18%) [4]	1 (10%) [1]
Infections	2 (9%) [2]	0 (0%) [0]

Musculoskeletal [#]	9 (41%) [19]	1 (10%) [2]
Respiratory	4 (18%) [4]	0 (0%) [0]
Skin	2 (9%) [2]	1 (10%) [1]
Other	9 (41%) [11]	5 (50%) [5]

*Only reporting by category, AE's greater than 5% (across both study arms) and infections; [#]includes arthralgia, myalgia, low back pain, orthopedic trauma, bursitis tendonitis, and muscle cramps; SAE=serious adverse event (infusion reaction, motor vehicle crash, chest pain, and abdominal pain).

Figure 2. Proportion of subjects maintaining serum urate (SU) less than 6 mg/dL illustrated over 24 week study period in mycophenolate mofetil (MMF) + pegloticase (Peg) vs. placebo (PBO) + pegloticase (Kaplan-Meier Estimates). One subject from PBO+pegloticase (PBO+Peg) group was censored at week 18, therefore the number of subjects for this group were 2 from week 20 to 24. However, the probability of "surviving" an interval did not change at a censored time, rather it changed at a failure time. Dashed line indicates period of pegloticase only therapy.

Figure 3. Proportion of RECIPE participants experiencing gout flares by treatment group over 24-week study period for the mycophenolate mofetil (MMF) + pegloticase (Peg) vs. placebo (PBO) + pegloticase study arms. *Dashed line indicates period of pegloticase only therapy.*

Supplemental Figure 1: Mean serum urate levels with standard deviation over 24-week study period in Mycophenolate mofetil (MMF) + pegloticase versus placebo (PBO) + pegloticase. *Dashed line indicates period of pegloticase only therapy.*

Supplemental Table 1. Randomization counts by site

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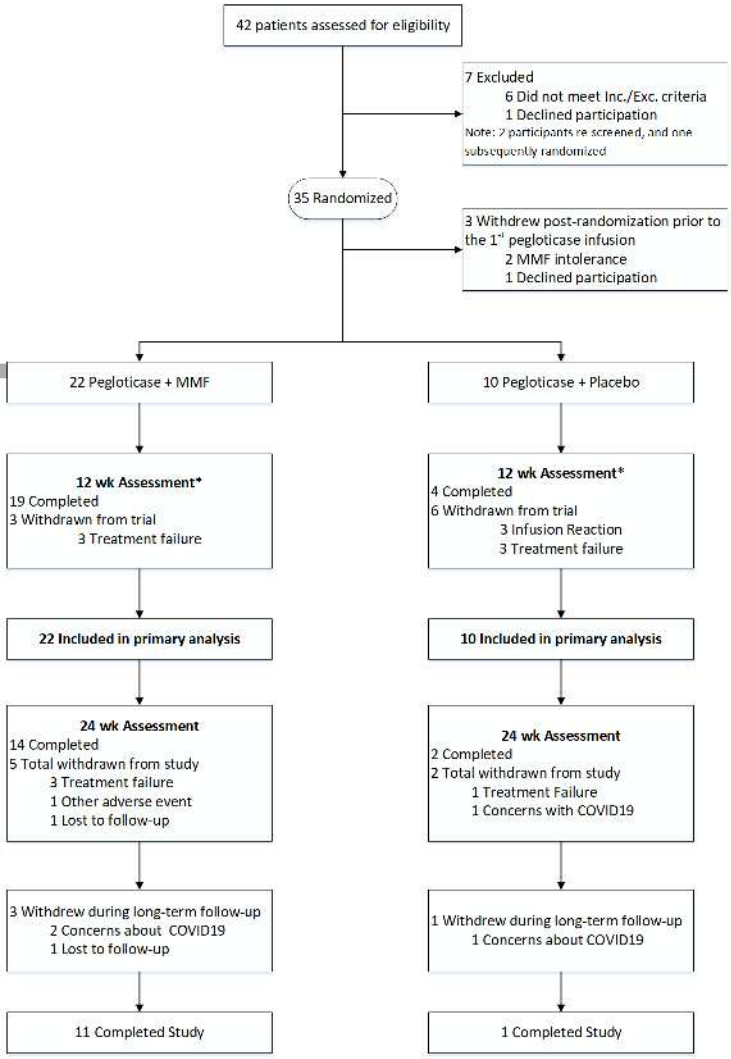

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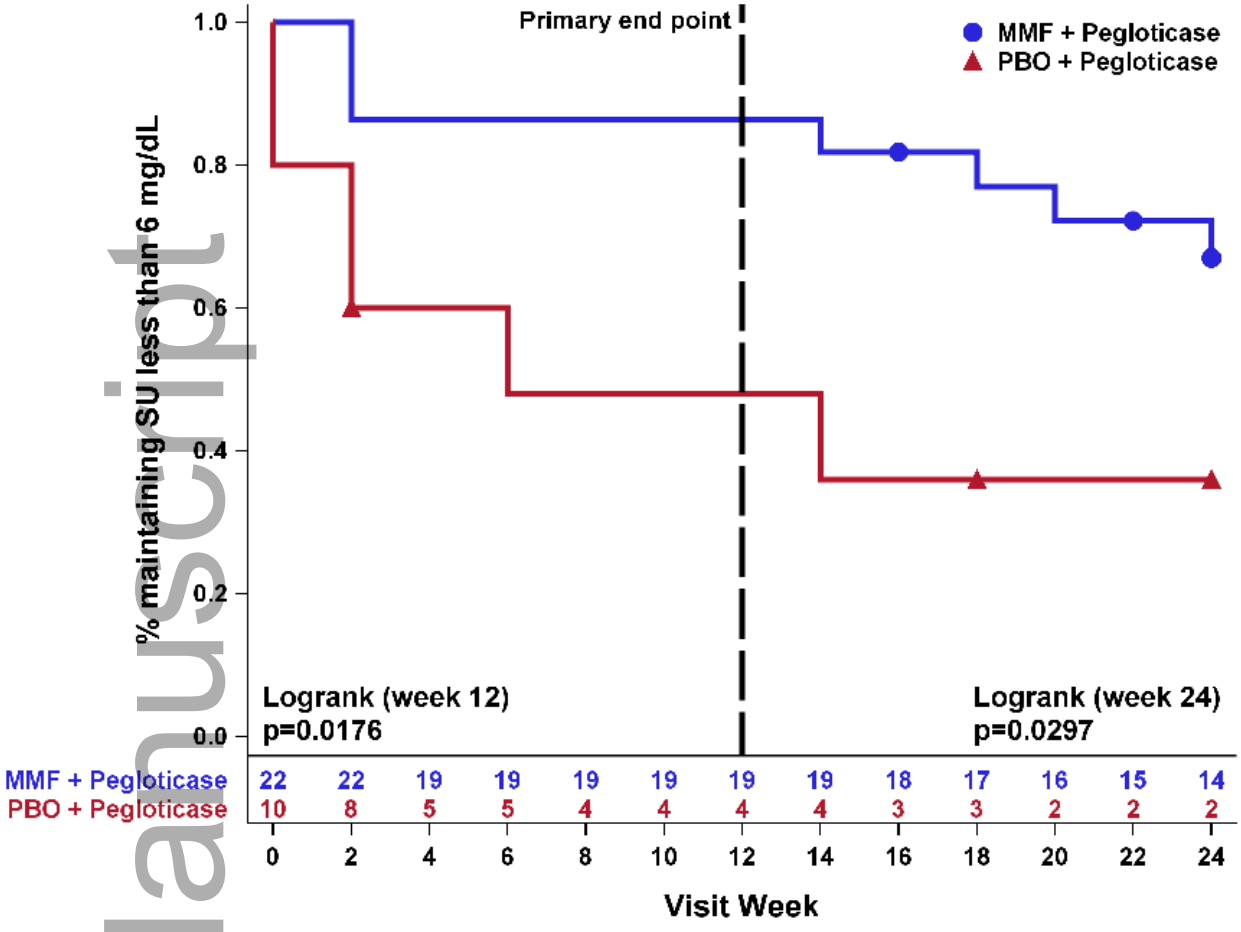

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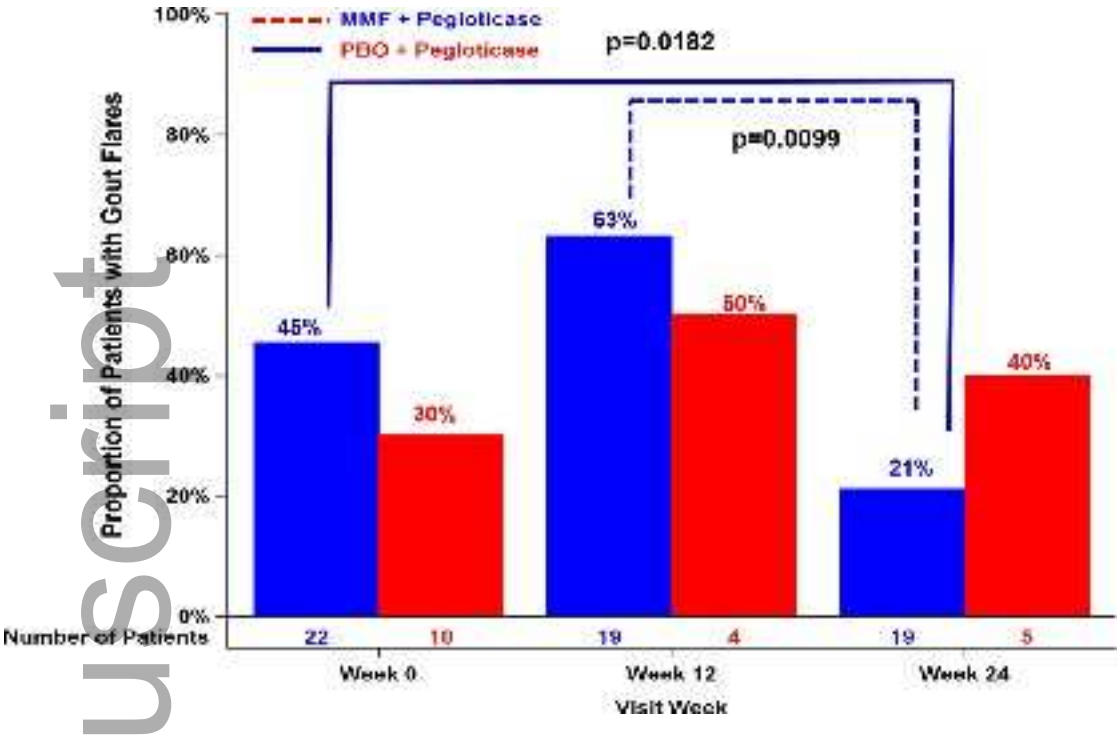

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