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Concise report

# Dual-energy CT assessment of rapid monosodium urate depletion and bone erosion remodelling during pegloticase plus methotrexate co-therapy

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## Abstract

**Objectives.** Pegloticase rapidly lowers serum urate in uncontrolled/refractory gout patients, with ≥1 tophus resolution in 70% of pegloticase responders and 28% of non-responders. Dual-energy computed tomography (DECT) non-invasively detects MSU deposition, including subclinical deposition, quantifies MSU volumes and depicts bone erosions. This report presents DECT findings in MIRROR open-label trial participants receiving pegloticase+MTX co-therapy.

**Methods.** Serial DECT scans were obtained during pegloticase (8 mg biweekly infusions)+oral MTX (15 mg/week) co-therapy. Bilateral hand/wrist, elbow, foot/ankle and knee images were analysed with default post-processing settings. MSU volumes were quantified and bone erosions were identified and evaluated for remodelling (decreased size, sclerosis, new bone formation). DECT and physical examination findings were compared.

**Results.** 2 patients underwent serial DECT. Patient 1 (44-year-old male) completed 52 weeks of pegloticase+MTX co-therapy (26 infusions). Baseline examination detected 4 tophus-affected joints while DECT identified 73 MSU-affected joints (total MSU volume: 128.76 $cm^3$). At end-of-treatment, there were no clinically-affected joints and 4 joints with DECT-detected MSU deposition. MSU volume decreased by 99% and bone erosion remodelling was evident. Patient 2 (51-year-old male) had 10 weeks of therapy (5 infusions), discontinuing because of urate-lowering response loss. Baseline examination detected 7 tophus-affected joints while DECT identified 55 MSU-affected joints (total MSU volume: 59.20 $cm^3$). At end-of-treatment, there were 5 clinically affected joints and 42 joints with DECT-detected MSU deposition. MSU volume decreased by 58% and bone erosion remodelling was evident.

**Conclusion.** DECT detected subclinical MSU deposition and quantified changes over time. Rapid tophus resolution and bone erosion remodelling occurred during pegloticase+MTX co-therapy.

**Trial registration.** ClinicalTrials.gov, https://clinicaltrials.gov, NCT03635957.

**Key words:** gout, pegloticase, tophus, dual-energy CT, monosodium urate deposition, bone erosion

CLINICAL SCIENCE

**Rheumatology key messages**

- DECT imaging depicted rapid depletion and resolution of MSU crystal deposition during pegloticase plus methotrexate co-therapy.
- Evidence of bone erosion remodelling, concomitant with MSU volume reduction, was observed during pegloticase plus methotrexate co-therapy.
- Pre-therapy, DECT identified up to 18 times more joints affected by MSU crystal deposition than physical examination.

## Introduction

Pegloticase (pegylated uricase) can rapidly lower serum urate in patients with refractory gout who no longer respond to or cannot tolerate oral urate-lowering therapies (ULTs) [1]. Further, resolution of at least one tophus after 6 months of therapy was observed in 70% of pegloticase responders and 28% of non-responders in phase 3 pivotal trials [2]. Dual-energy CT (DECT) can accurately and reliably identify MSU crystal deposition [3, 4], with the

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ability to detect subclinical tophi and measure the change in MSU deposition volume over time [5, 6]. Additionally, bone erosions, which have been previously linked to MSU deposition via DECT imaging [7], can be assessed and monitored with DECT [6, 8].

The MIRROR open-label (MIRROR OL) trial examined the efficacy and safety of adding oral MTX (15 mg/week) as co-therapy to a standard pegloticase treatment course (8 mg biweekly infusion), showing increased efficacy over monotherapy during month 6 of treatment (79% [9] *vs* 44% [1] response rate) with low rate of infusion reactions (IR) and no new safety concerns [9]. Two patients in the MIRROR OL trial underwent serial DECT imaging to monitor MSU volume changes and potential bone erosion remodelling. A prior radiological study of eight patients compared tophi and bone erosion scoring before and 12 months after intensive urate-lowering with pegloticase [10]. In contrast to that study, images in the MIRROR OL trial were obtained with DECT within weeks of initiating pegloticase plus MTX co-therapy and at multiple time points during treatment. The current report presents these serial imaging findings, which have increasing importance as MTX administration with pegloticase is increasingly adopted.

## Methods

The MIRROR OL trial was reviewed and approved by the Western Institutional Review Board (Puyallup, WA, USA). All patients provided written informed consent to participate in the trial, with separate written consent obtained for DECT imaging. All study conduct adhered to the tenets of the Declaration of Helsinki.

The MIRROR OL trial design and results are fully described elsewhere [9]. Briefly, all patients had uncontrolled/refractory gout (defined as serum urate $\geq$6 mg/dl with ULT use, ULT intolerance or functionally limiting tophi) and underwent up to 52 weeks of treatment with pegloticase (8 mg biweekly infusions) plus oral MTX (15 mg/week) co-therapy. Serial DECT scans (Somatom Definition AS+; Siemens Healthineers, Erlangen, Germany) from bilateral hand/wrist, elbow, foot/ankle and knee were obtained at baseline (Day 1) and Weeks 24, 36 and 52 (or Early Termination). All imaging was performed at a single study site using standardized data acquisition and image reconstruction settings, and DECT images were post-processed using a proprietary software (syngo.via; Siemens Healthineers) with the vendor's default settings for gout. They were then interpreted by a single independent radiologist for number of joints affected by MSU, MSU deposition volume and presence of bone erosions. Special care was taken to remove DECT artefacts commonly encountered with the gout application profile [11].

Authors experienced in DECT image interpretation (N.D., F.B., A.K.) examined up to three of the largest and discrete bone erosions of each imaged region (right knee, ankle, foot, elbow, wrist, hand; left knee, ankle, foot, elbow, wrist, hand; maximum of 36 evaluated erosions) for evidence of bone remodelling (decreased erosion size, increased sclerosis or new bone formation) for baseline and end-of-therapy images. The size of each evaluated erosion was measured using digital callipers. Authors independently examined images and a consensus was reached through discussion on the presence/absence of each bone remodelling criteria. Sites of MSU deposition and overall MSU volume per extremity were also assessed. The number of joints with MSU deposition on DECT was compared with the number of joints affected by tophus, as noted on physical examination.

## Case descriptions

The modified intent-to-treat population of the MIRROR OL trial, defined as all patients receiving at least one pegloticase infusion, included 14 patients [9]. A single trial site had DECT capabilities and had 2 patients initiate pegloticase plus MTX treatment. Both patients underwent serial DECT imaging and are presented here (Table 1).

### Patient 1

Patient 1 was a 44-year-old Asian male with a 25-year history of gout and a serum urate of 11.4 mg/dl at baseline. The patient reported 12 gout flares in the 12 months prior to screening and clinical examination revealed 4 tophus-affected joints and 4 tender or swollen joints. DECT imaging showed 73 joints with MSU deposition and a total MSU volume of 128.76 $cm^3$ (Table 1). Following study therapy initiation, serum urate rapidly declined to below quantification limits (BQL, $<$0.3 mg/dl), remaining BQL during the 52-week treatment period (26 pegloticase infusions received, treatment responder; Table 1). At Week 52, no tophi-affected or tender or swollen joints were identified. Adverse events during treatment included 2 gout flares during Weeks 4 and 6 of MTX plus pegloticase co-treatment.

With serum urate lowering, there was progressive MSU volume decrease on serial DECT imaging (Fig. 1), and, after 24 weeks (first intra-therapy imaging) and 52 weeks of pegloticase plus MTX co-therapy, overall MSU volume had decreased by 91% and 99%, respectively (Week 24 MSU volume: 11.42 $cm^3$; Week 52 MSU volume: 1.33 $cm^3$). MSU depletion occurred across all joints imaged, with an average MSU volume reduction of 99% $\pm$1% per joint. At Week 52, DECT imaging revealed 4 joints with MSU deposition, but no tophus-affected joints were noted on clinical examination. A total of 32 bone erosions were evaluated, none of which had completely resolved at Week 52 (Fig. 1). However, 31 (96.9%) of these erosions showed evidence of remodelling after 52 weeks of pegloticase + MTX co-therapy. More specifically, 31 erosions (96.9%) had a decrease in size (total erosion volume decreased by 55.1%), 24 erosions (75.0%) had increased sclerosis and 23 erosions (71.9%) had new bone formation. Further, the mean and maximum bone sclerosis density

TABLE 1 Clinical and DECT joint assessments in patients concomitantly treated with pegloticase (8 mg biweekly infusions) and oral methotrexate (15 mg/week)

| Patient 1: 44-year-old male, 26 biweekly pegloticase infusions | Baseline | Week 24 | Week 36 | Week 52 |
|---|---|---|---|---|
| Laboratory and clinical assessments | | | | |
| Serum urate, mg/dL | 11.4 | <0.3 | <0.3 | <0.3 |
| Joints affected by tophus, *n* | 4 | 0 | 0 | 0 |
| Tender or swollen joints | 4 | 0 | 0 | 0 |
| DECT assessments | | | | |
| Number of joints with MSU deposition | 73 | 24 | 11 | 4 |
| Total MSU volume, $cm^3$ | 128.76 | 11.42 | 4.05 | 1.33 |
| Right elbow | 4.50 | 0.16 | 0.02 | 0.00 |
| Right foot and ankle | 55.13 | 4.56 | 1.50 | 0.67 |
| Right hand and wrist | 5.90 | 0.09 | 0.01 | 0.00 |
| Right knee | 16.90 | 2.36 | 0.81 | 0.35 |
| Left elbow | 3.69 | 0.44 | 0.27 | 0.07 |
| Left foot and ankle | 17.70 | 0.66 | 0.26 | 0.10 |
| Left hand and wrist | 2.37 | 0.02 | 0.00 | 0.00 |
| Left knee | 22.57 | 3.13 | 1.18 | 0.14 |
| Evidence of bone remodelling, % erosions ($n = 32$) | – | – | – | 100% |
| Decrease in size, % erosions | – | – | – | 96.9% |
| Decrease in total erosion volume, % decrease | – | – | – | 55.1% |
| Increased sclerosis, % erosions | – | – | – | 75.0% |
| New bone formation, % erosions | – | – | – | 71.9% |
| **Patient 2: 51-year-old male, 5 biweekly pegloticase infusions** | **Baseline** | **Week 6** | **Week 8** | **Week 10** |
| Laboratory and clinical assessments | | | | |
| Serum urate, mg/dL | 9.4 | <0.3 | 8.9 | 8.1 |
| Joints affected by tophus, *n* | 7 | – | – | 5 |
| Tender or swollen joints, *n* | 0 | – | – | 2 |
| DECT assessments | | | | |
| Number of joints with MSU deposition | 55 | – | – | 42 |
| Total MSU volume, $cm^3$ | 59.20 | – | – | 25.07 |
| Right elbow | 6.85 | – | – | 2.29 |
| Right foot and ankle | 7.53 | – | – | 2.68 |
| Right hand and wrist | 2.51 | – | – | 0.35 |
| Right knee | 9.20 | – | – | 5.08 |
| Left elbow | 10.18 | – | – | 4.92 |
| Left foot and ankle | 7.83 | – | – | 1.73 |
| Left hand and wrist | 4.22 | – | – | 1.00 |
| Left knee | 10.88 | – | – | 7.02 |
| Evidence of bone remodelling, % erosions ($n = 25$) | – | – | – | 56.0% |
| Decrease in size, % erosions | – | – | – | 52.0% |
| Decrease in total erosion volume, % decrease | – | – | – | 26.7% |
| Increased sclerosis, % erosions | – | – | – | 44.0% |
| New bone formation, % erosions | – | – | – | 4.0% |

Baseline: last observation prior to first pegloticase infusion. DECT, dual-energy CT.

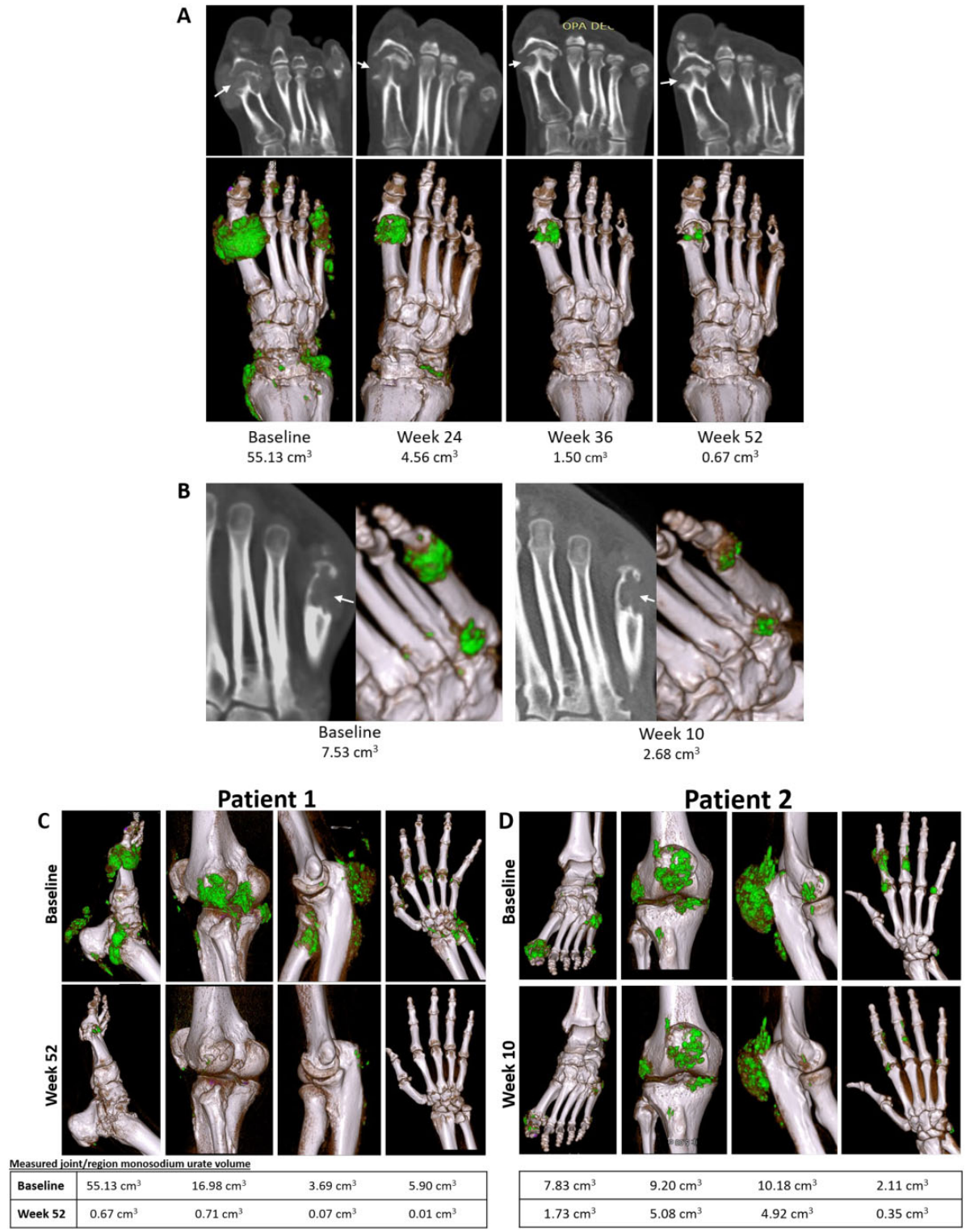
in the first metatarsophalangeal joint increased by up to 5.4% and 7.3% in the right foot and up to 32.7% and 10.2% in the left foot, respectively, following 52 weeks of treatment.

## Patient 2

Patient 2 was a 51-year-old Caucasian male with a 30-year history of gout and serum urate of 9.4 mg/dl at baseline. The patient reported 12 gout flares in the 12 months prior to screening and clinical examination revealed 7 tophus-affected joints and no tender or swollen joints. DECT imaging showed 55 joints with MSU deposition and a total MSU volume of 59.20 $cm^3$ (Table 1).

Following study therapy initiation, serum urate rapidly declined to BQL, remaining BQL through Week 6. At Weeks 8 and 10, pre-infusion serum urate was >6 mg/dl, indicating loss of treatment response and a potentially increased risk for IR with additional pegloticase therapy [12]. As specified in the trial protocol, study treatment was stopped (with the final infusion at Week 8; a total of 5 pegloticase infusions received) and an Early Termination visit, which included DECT imaging,

**Fig. 1** Serial DECT imaging of the right foot/ankle of Patient 1 (**A**) and Patient 2 (**B**)




Measured joint/region monosodium urate volume

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Baseline** | 55.13 cm³ | 16.98 cm³ | 3.69 cm³ | 5.90 cm³ | 7.83 cm³ | 9.20 cm³ | 10.18 cm³ | 2.11 cm³ |
| **Week 52** | 0.67 cm³ | 0.71 cm³ | 0.07 cm³ | 0.01 cm³ | 1.73 cm³ | 5.08 cm³ | 4.92 cm³ | 0.35 cm³ |

MSU deposition is depicted in green. Patient 2 prematurely discontinued therapy due to loss of urate-lowering effect. Patients 1 and 2 had a total MSU volume reduction of 99% and 58% during therapy, respectively, and first metatarsal head bone erosion (Patient 1) and fifth metatarsal bone erosion (Patient 2) remodelling (decreased erosion size, increased sclerosis or new bone formation) was evident (arrows). Other joints also showed MSU volume reduction and bone erosion remodelling during therapy (**C**), with MSU reduction/joint averaging 99%±1% and 63%±18% in Patients 1 and 2, respectively. DECT, dual-energy computed tomography; MSU, monosodium urate.

was performed at Week 10. The subject was considered a treatment non-responder, as defined by the study protocol. At Week 10, 5 tophi-affected and 2 tender or swollen joints were identified. Adverse events included 2 gout flares and post-root canal pain during the 4-week MTX run-in period and 5 gout flares (Weeks 3, 4, 7, 8 and 10), influenza infection and non-cardiac chest pain during the MTX + pegloticase co-treatment.

Comparison of baseline and Week 10 imaging revealed a 58% decrease in total MSU volume (Week 10 MSU volume: 25.07 $cm^3$; Table 1). MSU volume reduction occurred across multiple joints, with a mean reduction of 63% ± 18% per joint. At Week 10, DECT imaging revealed 42 joints with MSU deposition, but only 5 tophus-affected joints were noted on clinical examination. A total of 25 bone erosions were evaluated, none of which had completely resolved at Week 10 (Fig. 1). However, 14 (56.0%) of the erosions showed evidence of healing. More specifically, 13 erosions (52.0%) had a decrease in size (total erosion volume decrease of 26.7%), 11 erosions (44.0%) had increased sclerosis and one erosion (4.0%) had new bone formation.

## Discussion

DECT is emerging as a powerful tool to non-invasively detect and characterize MSU crystal deposition [3–5], bone erosion [7, 8] and ULT treatment response [6, 13]. The serial DECT images presented here demonstrate rapid MSU volume reduction during pegloticase plus MTX co-therapy over 52 weeks in a treatment responder (99% total MSU volume reduction, full treatment course) and over 10 weeks in a treatment non-responder (58% total MSU volume reduction, partial treatment course). It should be noted that residual DECT-based MSU-coded deposition at end of treatment (52 weeks) might be artifactual in Patient 1, with detected MSU possibly representing low-concentration calcium, dense fibrotic scar tissue or other tissue/material instead of true MSU deposition. Using dual thresholds (i.e. dual-energy ratios) during DECT post-processing, targeted at the crystal of interest, would have allowed a more accurate quantification of MSU deposition volumes, as recently demonstrated in a phantom study [14]. However, the default settings were considered acceptable here for measuring the percentage change in MSU volumes over time. Both patients also had a reduction in the number of tophus-affected joints on clinical examination.

Prior to pegloticase plus MTX co-therapy, DECT identified up to 18 times more joints affected by gout than physical examination. This is in agreement with a prior study also showing higher sensitivity of DECT compared with physical examination for detecting tophi [4]. Findings in the current cases are also in agreement with previous publications on DECT-evaluated MSU deposition changes with ULT. One publication reported MSU deposition before and after short-term pegloticase monotherapy (mean treatment of 5 infusions over 13 weeks), showing a mean MSU volume reduction of 95% in treatment responders ($n = 5$) and 48% in partial responders (premature pegloticase discontinuation due to loss of urate-lowering efficacy and allergic reaction, $n = 5$) [13]. Another publication reported a single case of marked MSU deposition reduction (>99%) over the 16 months following the addition of benzbromarone to febuxostat therapy [15]. Two larger studies demonstrated MSU volume reductions after 2 years of treat-to-target allopurinol (28% reduction, $n = 42$) [6] or treat-to-target ULT (allopurinol or febuxostat; reduction not quantified, $n = 187$) [16]. The current report builds upon these findings, adding evidence of rapid urate depletion accompanied by bone erosion improvements during the first weeks-to-months of intensive urate-lowering. Further, MSU volume reductions were relatively uniform across examination sites.

Tophi are associated with bone erosions [7, 17], with a strong correlation between tophus volume and bone erosion volume on DECT imaging [18, 19]. The DECT findings presented here are consistent with this association and suggest that bones can begin to remodel (decreased erosion size, increased sclerosis or new bone formation) as MSU deposition resolves during pegloticase plus MTX co-therapy. This is in agreement with a prior radiographic assessment showing evidence of structural improvements in bone erosions with pegloticase treatment [10]. However, the current study is the first to examine serial DECT images within the first 12 months of pegloticase therapy. One prior study did show bone erosion scoring improvements following intensive urate-lowering with pegloticase, but that study used radiography to evaluate bone erosions and did not include MSU volume measurements [10]. Further, these radiographic images were obtained prior to pegloticase therapy and 12 months later (5 patients also had 24-month images). Therefore, this is the first study to directly document concomitant MSU reduction and bone erosion remodelling within weeks of initiating pegloticaseplus MTX co-therapy. The previously mentioned DECT study by Dalbeth *et al.* [7] showed a physical correlation between MSU deposit and bone erosion location. However, that study did not include serial DECT images and, therefore, did not include longitudinal analyses. Though MTX has no known effects on gout or MSU crystals, better understanding crystal debulking and bone erosion healing during pegloticase plus MTX co-therapy is of growing importance as this treatment paradigm is increasingly adopted.

The two cases presented here support the need for further serial DECT studies that examine the relationship between MSU deposition volume and bone erosion in a larger number of gout patients being treated with ULT. Such imaging is currently being analysed in a subset of patients who participated in the MIRROR randomized controlled trial (RCT), which directly compared pegloticase plus MTX co-therapy to pegloticase therapy plus placebo co-therapy (MIRROR RCT, ClinicalTrials.gov registration: NCT03994731).

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*Ethics*: The MIRROR open-label trial protocol was reviewed and approved by the Western Institutional Review Board (Puyallup, WA, USA). All subjects provided informed consent to participate in the trial, with separate consent obtained to perform serial DECT imaging at specified timepoints during the trial. All study conduct adhered to the tenets of the Declaration of Helsinki.

## Data availability statement

Horizon is committed to responsibly sharing data from the clinical trials we sponsor. Access to anonymized, individual and trial-level data (analysis data sets) may be granted to qualified researchers for independent scientific research, provided the trials are not part of an ongoing or planned regulatory submission (including clinical trial data for unlicensed products and indications). Data may be requested by submitting a research proposal and Statistical Analysis Plan and will be provided following review and approval of the plan and execution of a Data Sharing Agreement. For more information, or to submit a request, please submit to: medicalinformation@horizontherapeutics.com.

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