Magnetic Resonance Imaging (MRI) Results Following Discontinuation of Methotrexate in Rheumatoid Arthritis Treated with Subcutaneous Tocilizumab: The COMP-ACT MRI Substudy

Charles Peterfy, Joel Kremer, William Rigby, Nora Singer, Christine Birchwood, Darcy Gill, William Reiss, Jinglan Pei, and Margaret Michalska

ABSTRACT. Objective. To assess differences in joint damage and inflammation using magnetic resonance imaging (MRI) between patients with rheumatoid arthritis (RA) who achieved low disease activity with tocilizumab (TCZ) + methotrexate (MTX) and subsequently continued or discontinued MTX.

Methods. In the COMP-ACT trial, US patients with RA received subcutaneous TCZ 162 mg + MTX. Those who achieved 28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate (DAS28-ESR) ≤ 3.2 at Week 24 were randomized 1:1 (double-blind) to discontinue MTX (TCZ monotherapy; mono) or continue TCZ + MTX until Week 52. In a subset of patients, 1.5-Tesla MRI was used to obtain images of bilateral hands and wrists at weeks 24 and 40. Outcomes included changes in MRI-assessed synovitis, osteitis, erosion, and cartilage loss from Week 24 to Week 40, and in the proportion of patients with progression of each score.

Results. Of 296 patients who achieved DAS28-ESR ≤ 3.2 at Week 24, 79 were enrolled in the pilot MRI substudy and randomized to TCZ mono (n = 38) or TCZ + MTX (n = 41). Treatment with either TCZ mono or TCZ + MTX suppressed erosion progression, synovitis, osteitis, and cartilage loss. The proportion of patients with no progression in each outcome measure was similar between groups (range, TCZ mono: 84.8–97.0%; TCZ + MTX: 92.3–100%).

Conclusion. In a subset of patients who achieved low disease activity with TCZ + MTX, MRI changes were minimal in intraarticular inflammation and damage measures in patients who discontinued MTX versus those who continued TCZ + MTX. (First Release November 1 2019; J Rheumatol 2020;47:325–32; doi:10.3899/jrheum.180953)

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From Spire Sciences Inc., Boca Raton, Florida; Albany Medical College and The Center for Rheumatology, Albany, New York; Geisel School of Medicine, Dartmouth College, Lebanon, New Hampshire; Case Western Reserve University and MetroHealth System, Cleveland, Ohio; Genentech Inc., South San Francisco, California, USA.

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C. Peterfy is a consultant for Roche and an employee of Spire Sciences Inc. J. Kremer is a shareholder of Corrona LLC, and a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly and Co., Genentech Inc., GlaxoSmithKline, Pfizer, Regeneron, and Sanofi. W. Rigby is a consultant for Roche/Genentech. N. Singer is a consultant for Genentech. D. Gill, W. Reiss, J. Pei, and M. Michalska are employees of Genentech Inc. C. Birchwood was an employee of Genentech Inc. at the time of this study.

C. Peterfy, MD, Spire Sciences Inc.; J. Kremer, MD, Albany Medical College and The Center for Rheumatology; W. Rigby, MD, Geisel School of Medicine, Dartmouth College; N. Singer, MD, Case Western Reserve University and MetroHealth System; C. Birchwood, PhD, Genentech Inc.; D. Gill, BS, Genentech Inc.; W. Reiss, PharmD, Genentech Inc.; J. Pei, BS, Genentech Inc.; M. Michalska, MD, Genentech Inc.

Address correspondence to Dr. C. Peterfy, Spire Sciences Inc., 5314 Boca Marina Circle North, Boca Raton, Florida 33487, USA.

E-mail: Charles.peterfy@spiresciences.com

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Magnetic resonance imaging (MRI) can detect changes in bone erosion with greater sensitivity than radiography and is an effective way to assess synovitis and osteitis in patients with rheumatoid arthritis (RA)^{1,2,3}. Synovitis and osteitis have been shown to predict subsequent radiographic progression and structural deterioration in patients with RA^{4,5,6,7}. Further, patients with RA who achieve remission based on the 28-joint count Disease Activity Score (DAS28) may still have synovitis, which in turn may lead to joint damage^{6,8,9}, and possibly result in permanent disability^{8,10,11}. The sensitivity of MRI allows for early detection of RA disease progression, provides a more sensitive evaluation of disease activity, and can detect therapeutic response in a shorter observation time^{1,12,13}.

Although methotrexate (MTX) is often administered in combination with biologics to treat RA, it may be discontinued because of intolerance or to reduce the medication burden. Real-world studies have shown that about one-third of patients with RA who require biologic therapy receive it as monotherapy^{14,15,16}, often because of MTX intolerance.

erance^{17,18,19}. Tocilizumab (TCZ) is a humanized monoclonal antibody against the interleukin (IL)-6 receptor and has been proven to be safe and effective in patients with RA, either in combination with MTX or as monotherapy^{20–29}. Previous studies have shown that TCZ in combination with MTX or as monotherapy inhibits radiographic progression in patients with RA^{13,21,29,30}; however, changes in active intraarticular inflammation after discontinuation of MTX in patients achieving good clinical control with TCZ + MTX have not been evaluated. In addition, only 1 study has evaluated radiographic data in patients receiving subcutaneous TCZ (TCZ-SC)³¹, and only 1 study has evaluated joint damage using MRI in patients receiving TCZ-SC³⁰.

In a randomized, phase IV noninferiority study (COMP-ACT), patients with RA who achieved low disease activity (LDA) with TCZ + MTX and subsequently discontinued MTX had similar outcomes compared with patients who continued MTX³². The mean change in DAS28 calculated with erythrocyte sedimentation rate (DAS28-ESR) 16 weeks after discontinuation of MTX was similar between patients who received TCZ as monotherapy and those who received TCZ + MTX. The current substudy used MRI to assess differences in active intraarticular inflammation and joint damage by comparing the changes in MRI scores from Week 24 to Week 40 between patients with RA who had achieved LDA with TCZ + MTX and then either continued or discontinued MTX.

MATERIALS AND METHODS

Study design. COMP-ACT was a randomized, multicenter, double-blind, parallel-group, 52-week study (plus an 8-week followup) that compared TCZ + MTX with TCZ + placebo (TCZ monotherapy; mono) in patients with RA (Figure 1). This trial is registered on ClinicalTrials.gov: NCT01855789. A full description of the methods and patients has been described previously³². At baseline (Week 0), all patients received TCZ-SC 162 mg [weekly (qw) for patients weighing ≥ 100 kg or every 2 weeks (q2w) for patients weighing < 100 kg]; patients continued to receive their stable pre-baseline dose of open-label, oral MTX ≥ 15 mg/week. Patients receiving TCZ-SC q2w who did not achieve DAS28-ESR ≤ 3.2 at Week 12 could increase the dosing frequency to weekly. At Week 24, patients who achieved DAS28-ESR ≤ 3.2 were randomized 1:1 (double-blind) to either continue MTX (TCZ + MTX) or discontinue MTX (TCZ mono) through Week 52. A subset of these randomized patients was included in the MRI substudy.

This study was approved by the Copernicus Group Independent Review Board, Durham, North Carolina (tracking number INV2-13-154), and the institutional review boards and independent ethics committees of the investigational centers (160 centers with about 70 centers included in the MRI substudy). All patients provided written informed consent in accordance with the Declaration of Helsinki.

Patients. Patients aged ≥ 18 years and weighing ≤ 150 kg with moderate to severe RA (DAS28-ESR ≥ 4.4) according to the revised 1987 American College of Rheumatology criteria were included. Full inclusion and exclusion criteria have been described³². Patients were required to have an inadequate response to MTX, and up to about 20% of patients could have received a single tumor necrosis factor inhibitor ≥ 6 months prior to screening. Patients were enrolled in the MRI substudy based on whether their location of enrollment was an MRI study site. MRI participation was a stratification factor at the time of randomization.

Assessments and outcomes. Both hands and wrists were imaged using

1.5-Tesla (T) MRI at weeks 24 and 40 only (no MRI was performed at baseline). The dominant hand was defined as the operant hand generally used for performing fine motor skills tasks (e.g., writing). All participating sites received training related to MRI technique and patient positioning. A commercial coil was used, which allowed coverage of the entire hand and wrist in a single field of view. A specially designed acrylic M-frame was used to facilitate proper and reproducible positioning³³. The MRI protocol included coronal short-tau inversion recovery (STIR); coronal T1-weighted, 3-D gradient-echo with spectral fat suppression; and axial STIR; no gadolinium contrast was used. The right hand and wrist were imaged simultaneously followed by the left hand and wrist.

Two independent radiologists evaluated the images at a central reading facility using the Outcome Measures in Rheumatology Clinical Trials–Rheumatoid Arthritis Magnetic Resonance Imaging Score (OMERACT-RAMRIS) system³⁴ to assess bone erosion, synovitis, and osteitis, and the 9-point cartilage loss scale (CARLOS) to assess cartilage loss³⁵. Radiologists were blinded to visit order and treatment group. Changes in bone erosion, synovitis, osteitis, and cartilage loss occurring between Week 24 and Week 40 were measured. The smallest detectable change (SDC) was calculated to differentiate true change from interreader variability and was based on the SD of the differences between the change scores of the 2 MRI reviewers³⁶. The thresholds for significant change at the individual patient level based on the SDC were 1.0 for bone erosion, 1.4 for osteitis, 0.9 for synovitis, and 0.6 for cartilage loss.

Statistical analyses. Based on historical data from the ACT-RAY study (0.2T MRI of the more symptomatic hand and wrist)¹³, it was established that 30 patients per arm would permit estimation of the 95% CI for group differences in the change in bone erosion score from Week 24 to Week 40 to within ± 1.7 units, synovitis score to within ± 0.98 units, and osteitis score to within ± 2.88 units; no historical data were available at the time of study design to evaluate the efficacy of the planned sample size for the MRI endpoint of cartilage loss. Baseline demographics and clinical characteristics were summarized using descriptive statistics. The mean changes in MRI scores from Week 24 to Week 40 for each treatment arm and the difference in the means between treatment arms were estimated based on analysis of covariance adjusted for the stratification factors used in randomization. Cumulative probability plots of the changes in scores (bone erosion, synovitis, osteitis, and cartilage loss) from Week 24 to Week 40 were produced. The number and percentage of patients with progression from Week 24 to Week 40 on each assessment as determined by worsening that was greater than the SDC were summarized.

RESULTS

Baseline demographics and clinical characteristics. Of the 296 patients who achieved DAS28-ESR ≤ 3.2 at Week 24 and were randomized to receive either TCZ mono or TCZ + MTX, 79 were included in the MRI substudy. A total of 38 patients received TCZ mono, and 41 received TCZ + MTX. Baseline demographics were similar between treatment groups in the MRI substudy and between patients in the MRI substudy and the overall study population (Table 1).

MRI analysis. At Week 24 (randomization), MRI scores were similar between treatment groups (Table 2). At Week 40, patients receiving either TCZ mono or TCZ + MTX had minimal numerical changes in synovitis, osteitis, bone erosion, or cartilage loss (Table 3). The 95% CI of the difference in the changes in MRI scores between the TCZ mono and TCZ + MTX groups crossed zero for bone erosion, synovitis, osteitis, and cartilage loss, suggesting that there was no clinically meaningful difference between groups. Although data from ACT-RAY were used to estimate the

Figure 1. Study design. Open-label TCZ-SC was administered for the entire study duration; MTX discontinuation was maintained in a blinded fashion after Week 24. * If patient weight ≥ 100 kg, start TCZ-SC qw. † If DAS28-ESR > 3.2 , increase frequency to qw. DAS28-ESR: 28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate; mono: monotherapy; MRI: magnetic resonance imaging; MTX: methotrexate; q2w: every 2 weeks; qw: every week; OL: open label; R: randomization; SC: subcutaneous; TCZ: tocilizumab.

Figure 2. Individual patient bilateral MRI scores. A. Bone erosion. B. Synovitis. C. Osteitis. D. Cartilage loss. Mono: monotherapy; MRI: magnetic resonance imaging; MTX: methotrexate; SDC: smallest detectable change; TCZ: tocilizumab.

Figure 2. Continued.

sample size needed to permit estimation of the 95% CI to detect group differences, the present study was not powered to discriminate statistical differences in the changes between these groups. MRI results were consistent for bilateral hands and wrists and for the dominant hand and wrist, but the changes in erosion and osteitis were numerically slightly greater on the dominant side. Cumulative probability plots showed no major outliers for change greater than the SDC in erosion, synovitis, and cartilage loss (Figure 2), but 2 patients in the TCZ mono group showed relatively large changes in osteitis (5.75 and 9.25; Figure 2C).

The majority of patients in both treatment groups had no MRI progression in both hands at Week 40; this was also seen in the dominant hand and wrist (Figure 3). Differences between groups in the proportion of patients with no progression in the dominant hand in each outcome measure were small (range, TCZ + MTX: 92.3%-100%; TCZ mono: 84.8%-97.0%).

DISCUSSION

This COMP-ACT trial substudy used MRI to measure bone erosion, synovitis, osteitis, and cartilage loss. Treatment with

Table 1. Baseline demographics and clinical characteristics.

Characteristics	TCZ Mono, n = 38	TCZ + MTX, n = 41	Total Patients, N = 294*
Female, n (%)	29 (76.3)	30 (73.2)	220 (74.8)
Age, yrs	54.2 (14.0)	58.3 (11.3)	55.5 (12.6)
Duration of RA, yrs	6.8 (6.4)	7.0 (8.3)	6.8 (7.7)
RF-positive, n (%)	33 (86.8)	31 (75.6)	212 (72.1)
ACPA-positive, n (%)	33 (86.8)	31 (75.6)	223 (75.9)
Weight, kg	79.1 (18.7)	78.6 (14.7)	81.7 (18.8)
BMI, kg/m ²	29.7 (6.8)	28.2 (5.2)	29.9 (6.4)
No. previous DMARD	1.3 (0.4)	1.3 (0.5)	1.2 (0.5)
Baseline MTX dose, mg/week	18.0 (3.0)	18.5 (3.1)	17.9 (3.2)
No. previous TNFi	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)
Oral corticosteroid use, n (%)	15 (39.5)	17 (41.5)	111 (37.8)
Baseline corticosteroid dose, mg/day	6.4 (2.7)	6.6 (2.5)	6.6 (2.7)
DAS28-ESR	6.4 (1.1)	6.2 (0.9)	6.3 (0.9)
CDAI	37.4 (12.1)	38.5 (13.5)	38.2 (12.3)
SDAI	39.3 (12.3)	39.3 (13.7)	39.3 (12.5)

Values are mean (SD) unless otherwise specified. * Two of the 296 randomized patients were not treated after Week 24; therefore, 294 randomized patients were included in the intent-to-treat population. ACPA: anticyclic citrullinated peptide antibody; BMI: body mass index; CDAI: Clinical Disease Activity Index; DAS28-ESR: 28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drug; mono: monotherapy; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor.

Table 2. Bilateral MRI scores* at randomization (Week 24). Values are mean (SD).

	TCZ Mono, n = 38	TCZ + MTX, n = 41
Bone erosion (0–250)	9.1 (7.9)	10.7 (11.2)
Synovitis (0–24)	2.3 (2.0)	3.4 (3.3)
Osteitis (0–75)	2.3 (3.9)	2.5 (3.1)
Cartilage loss (0–100)	4.7 (6.4)	5.7 (8.2)

* Bilateral MRI scores were averaged over both hands. Mono: monotherapy; MRI: magnetic resonance imaging; MTX: methotrexate; TCZ: tocilizumab.

Table 3. Changes in MRI scores from Week 24 to Week 40 in patients receiving TCZ in combination with MTX or TCZ as monotherapy.

Mean Change from Week 24 to Week 40*	TCZ Mono, n = 38	Both Hands TCZ + MTX, n = 41	Difference, TCZ Mono Minus TCZ + MTX (95% CI)	TCZ Mono, n = 38	Dominant Hand TCZ + MTX, n = 41	Difference, TCZ Mono Minus TCZ + MTX (95% CI)
Bone erosion (0–250)	0.18 (0.19)	−0.06 (0.18)	0.24 (−0.21 to 0.68)	0.49 (0.25)	0.06 (0.24)	0.43 (−0.14 to 1.01)
Synovitis (0–24)	−0.18 (0.15)	−0.24 (0.15)	0.06 (−0.30 to 0.41)	−0.11 (0.12)	−0.22 (0.12)	0.11 (−0.18 to 0.40)
Osteitis (0–75)	0.37 (0.36)	−0.16 (0.34)	0.53 (−0.30 to 1.36)	0.69 (0.54)	−0.39 (0.52)	1.07 (−0.18 to 2.33)
Cartilage loss (0–100)	−0.03 (0.15)	0.20 (0.14)	−0.23 (−0.58 to 0.11)	−0.05 (0.19)	0.11 (0.18)	−0.16 (−0.59 to 0.27)

Values are mean (SE) unless otherwise indicated. * ANCOVA model for estimated means includes Week 24 bone erosion as a covariate, treatment group, and the following randomization stratification factors: DAS28-ESR remission status at Week 24 (< 2.6 or ≥ 2.6 to ≤ 3.2), patient TNFi exposure (yes or no), and baseline weight-by-dosing group (< 80 kg q2w, 80 to < 100 kg q2w, 80 to < 100 kg qw, or ≥ 100 kg qw). Week 24 MRI scores were subtracted from Week 40 MRI scores, and a negative score indicates an improvement. DAS28-ESR: 28-joint count Disease Activity Score calculated with erythrocyte sedimentation rate; mono: monotherapy; MRI: magnetic resonance imaging; MTX: methotrexate; q2w: every 2 weeks; qw: once a week; SE: standard error; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor.

either TCZ + MTX or TCZ mono in patients with RA who had achieved LDA with TCZ + MTX suppressed synovitis, osteitis, cartilage loss, and erosion progression. Although therapy with TCZ + MTX showed numerically greater suppression of bone erosion (difference of 0.24 on a scale of 0–250), synovitis (0.06 on a scale of 0–24), osteitis (0.53 on a scale of 0–75), and cartilage loss (−0.23 on a scale of 0–100; Table 3) compared with TCZ mono, the study was not powered to discriminate small differences between the 2 groups.

The present study differs from prior MRI studies involving TCZ mono. In the phase IIb ACT-RAY study, which included patients with inadequate response to MTX (DAS28 > 4.4 at baseline), a subset of patients underwent MRI of the more symptomatic hand and wrist at weeks 0, 2, 12, and 52, and radiography of the hands/wrists and feet at weeks 0, 24, and 52¹³. Patients were receiving MTX prior to baseline and either switched to intravenous (IV) TCZ mono (n = 32) or continued MTX and added TCZ-IV (TCZ + MTX; n = 31), as opposed to the present study in which patients achieved LDA while receiving TCZ + MTX then discontinued MTX (Week 24). In the open-label AC-CUTE study, 52 patients received either TCZ-SC mono or TCZ in combination with MTX or other conventional synthetic disease-modifying antirheumatic drugs (DMARD). Patients underwent MRI of the dominant hand and radiography of the hands, wrists, and feet at weeks 0 and 24³⁰. Erosion and cartilage loss scores at Week 24 in the present study were similar to those at baseline in the AC-CUTE study (erosion: 8.4–9.9; cartilage loss: 4.8–9.2), but erosion scores were lower than those at baseline in the ACT-RAY MRI substudy (16.0–19.4)^{13,30}. The synovitis and osteitis scores at Week 24 in the present study were also less than half those observed at baseline in the prior studies (ACT-RAY synovitis: 7.2–7.4; ACT-RAY osteitis: 7.8–11.1; AC-CUTE synovitis: 4.3–4.6; AC-CUTE osteitis: 5.3–7.3). This is not surprising because the patients in COMP-ACT had already achieved clinical LDA with TCZ therapy by Week 24.

Figure 3. Percentage of patients not progressing more than the SDC in the dominant hand and wrist at Week 40. Mono: monotherapy; MTX: methotrexate; SDC: smallest detectable change; TCZ: tocilizumab.

In the present study, MRI scores were consistent between both hands and wrists and the dominant hand and wrist; however, the changes in erosion and osteitis, the precursor to erosion, were numerically slightly greater on the dominant side. The magnitude of the changes in synovitis and osteitis in the present study was less than those observed in the ACT-RAY MRI substudy and AC-CUTE study^{13,30}. Each of those 2 studies showed significant decreases of about 2 units for synovitis and 4 units for osteitis, whereas the changes in the present study were small (< 1 unit). This difference is likely due to lower baseline severity of inflammation in these patients who had achieved LDA after 24 weeks of TCZ + MTX therapy in the open-label phase of the present study.

The difference in magnitude of changes also may be related to the shorter 16-week interval between MRI imaging in the present study than in prior studies. In the ACT-RAY MRI substudy, the most significant differences in synovitis and osteitis scores were measured after 52 weeks of therapy, but improvements in synovitis and osteitis scores were observed as early as 2 weeks. In the AC-CUTE study, MRI changes were measured after 24 weeks. The smaller decreases observed in synovitis may have been related to the present study not using gadolinium contrast, which increases sensitivity and specificity for synovitis. However, a smaller decrease was also seen for osteitis, which is most sensitively

detected with gadolinium non-enhanced STIR imaging used in this study.

Including cartilage loss and bone erosion in this study allowed full MRI evaluation of structural damage to the joints, analogous to the radiographic total Sharp score used in clinical trials of patients with RA³⁷. A large study of data pooled from several clinical trials concluded that cartilage loss was, in fact, a stronger determinant of disability than was erosion⁸. Additionally, while erosion and cartilage loss usually covary, the link between the two is not sufficiently strong to ensure that an effect observed on one is invariably happening to the other. Progression of erosion and joint space narrowing did not occur at the same rate in the ASPIRE study of infliximab³⁸ and in a study of denosumab⁷. In both studies, erosion was strongly inhibited, whereas joint space narrowing continued to progress^{7,38}.

The present study is unique in that bilateral hands and wrists were imaged using MRI. Patients with RA are characterized by symmetrical joint involvement, and both physical examination and radiographs are often performed on the bilateral hands and wrists. However, most clinical trials of RA using MRI have imaged only one side, usually the clinically most severe or dominant side^{13,30}. The minimal clinical differences between the dominant hand and both hands in the present study are supported by a previous radiographic study

indicating more symmetry as RA progresses³⁹. However, a large study evaluating handedness and severity of affected joints in patients with RA showed that the joints on the dominant side of right-handed patients were clinically and radiographically more affected; a similar pattern was seen in left-handed patients, but the sample size was small⁴⁰. In contrast, a study using 3.0T MRI to image bilateral hands and wrists in patients with RA (median disease duration of 48 months) showed that the dominant hand was not always more severely affected than the nondominant hand based on MRI scores⁴¹. In addition, the clinically most affected hand as chosen by patient complaint and physical examination may not be the most affected based on MRI. The aforementioned study reported poor concordance between physical examination and MRI scores; linear regression showed that the clinically more severe hands could not represent the contralateral hand to evaluate RAMRIS⁴¹. Imaging bilateral hands and wrists with MRI may prevent misdiagnosis that may result if only the dominant or most clinical hand and wrist are imaged.

Owing to the small sample size and small differences in the changes among the MRI features examined, this MRI substudy was not powered to show a clinically significant difference between treatments with TCZ + MTX and TCZ mono. In addition, gadolinium-based contrast was not used in this study, which might have decreased the sensitivity and specificity, particularly for synovitis evaluations; however, not using gadolinium contrast allowed reduction of the overall imaging time. Further, no baseline MRI was performed before treatment with TCZ, limiting the ability to assess the effect of TCZ on joint damage prior to the first MRI assessment. Finally, it is possible that 16 weeks is not long enough to determine the longterm effect of MTX discontinuation on joint damage.

In a subset of patients who achieved LDA with TCZ + MTX and were included in this MRI pilot substudy, minimal further MRI-assessed changes were observed in those who discontinued MTX and those who continued MTX.

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