ORIGINAL ARTICLE

Improved disease activity with fosdagrocorat (PF-04171327), a partial agonist of the glucocorticoid receptor, in patients with rheumatoid arthritis: a Phase 2 randomized study

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Abstract

Aim: To assess efficacy and safety of fosdagrocorat (PF-04171327), a potential dissociated agonist of the glucocorticoid receptor, in rheumatoid arthritis (RA) patients.

Methods: This multicenter, double-blind, parallel-group, active- and placebo-controlled Phase 2 study (NCT00938587) randomized 86 patients (1 : 1 : 1 : 1) to receive fosdagrocorat 10 mg, fosdagrocorat 25 mg, prednisone 5 mg or placebo, all with stable background methotrexate therapy. The primary outcome was change from baseline in Disease Activity Score of 28 joints (DAS28-4[C-reactive protein (CRP)]) after 2 weeks of treatment. Secondary outcomes included American College of Rheumatology (ACR) response rates, change from baseline in ACR core components and Health Assessment Questionnaire Disability Index.

Results: At week 2, improvements from baseline in DAS28-4(CRP) with fosdagrocorat 10 and 25 mg, prednisone 5 mg and placebo were -1.69, -2.22, -1.17 and -0.96, respectively, and were statistically significantly greater for both fosdagrocorat doses versus placebo ($P < 0.05$) and for fosdagrocorat 25 mg versus prednisone 5 mg ($P < 0.001$). The effects of fosdagrocorat on secondary outcomes were generally consistent with those observed for the primary outcome. Adverse events (AEs) were reported for eight (38%), three (14%), four (19%) and 12 (55%) patients treated with fosdagrocorat 10 and 25 mg, prednisone 5 mg and placebo, respectively. Most AEs were mild in severity. Four patients discontinued treatment due to AEs (fosdagrocorat 10 mg, $n = 2$; placebo, $n = 2$). There were no serious AEs.

Conclusion: Fosdagrocorat 10 and 25 mg demonstrated efficacy in improving signs and symptoms in RA patients, with manageable AEs. Additional studies are needed to assess the longer-term safety and efficacy of fosdagrocorat.

Key words: arthritis, glucocorticoids, prednisone, randomized controlled trial, rheumatoid.

INTRODUCTION

Glucocorticoids (GCs) are well established in treating chronic inflammatory diseases, such as rheumatoid arthritis (RA), despite a profile of serious side effects.[1–3] Approximately two-thirds of patients with RA are treated with GCs at some point during their lifetime,[4] and systematic reviews of published studies support the effect of low-dose GCs in reducing signs and symptoms and slowing the progression of structural damage in RA.[5–7] The most commonly prescribed GC for RA is prednisone, which is converted to prednisolone, a full

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glucocorticoid receptor (GR) agonist.[8] The use of GCs in RA remains controversial due to the adverse effects associated with chronic GC use, such as osteoporosis, diabetes, adrenal suppression, weight gain, hypertension, mood disturbances, impaired wound healing and increased susceptibility to opportunistic infections.[9–12] Therefore, identifying a compound that has the anti-inflammatory effect of a GC with improved safety would offer a significant clinical advantage.

Studies carried out in preclinical models of inflammation have suggested that a novel class of drugs, dissociated agonists of the glucocorticoid receptor (DAGRs), may retain the anti-inflammatory effects mediated by GR protein interactions while avoiding some of the adverse events (AEs) caused by full GR agonists.[13–16] Fosdagrocorat (PF-04171327), a prodrug of PF-00251802, is under investigation as a potential non-steroidal DAGR. PF-00251802 is a selective, high-affinity partial agonist of the GR. In preclinical studies using cell culture and mouse models of RA, PF-00251802 manifested potent anti-inflammatory activity with likely dissociation from GC-induced adverse effects on bone and glucose metabolism.[17,18] In addition, in the lipopolysaccharide-induced mouse model of RA, fosdagrocorat demonstrated a four-fold dissociation, relative to prednisone, between efficacy in RA and inhibition of bone formation.[18]

Following on from preclinical models, a 2-week, Phase 1 multiple-dose study in healthy volunteers (NCT00812825) was performed to evaluate the safety, tolerability, pharmacokinetics (PK) and magnitude of potential dissociation of fosdagrocorat.[19] In this study, the assessment of dissociation was pre-specified to allow identification of the fosdagrocorat dose range where the effect on a biomarker of bone formation (osteocalcin) was equivalent to prednisone 5 mg once daily, and effects on counts of circulating white blood cells, a biomarker of anti-inflammatory activity, were equivalent to prednisone 20 mg once daily. In the dose range of 10–25 mg once daily, the impact of fosdagrocorat on biomarkers of adverse bone effects was similar to that of prednisone 5 mg once daily, whereas the effects on anti-inflammatory biomarkers were similar to those of prednisone 20 mg once daily. Based on these findings, further study to confirm the anti-inflammatory effects of fosdagrocorat on clinical endpoints in patients with RA is warranted.

The primary objective of the present 2-week Phase 2a study was to evaluate the efficacy and safety of fosdagrocorat relative to placebo and low-dose prednisone in patients with active RA and an inadequate response to methotrexate (MTX). The 2-week study duration was considered optimal in this instance, as fosdagrocorat was expected to have steroid-like rapidity of onset. Therefore, anti-inflammatory effects were expected to be apparent within this timeframe. The PK properties of fosdagrocorat and its effects on plasma cortisol levels are also reported. Two dosages of fosdagrocorat were assessed in this study, 10 mg and 25 mg once daily. The 25 mg dose was anticipated to provide significant anti-inflammatory activity while still maintaining dissociation relative to prednisone. The 10 mg dose was chosen to evaluate efficacy in RA at a dose with substantially lower potential for bone adverse effects compared with prednisone 5 mg. Prednisone 5 mg once daily was selected as an active comparator because this represents a clinically relevant dose used in patients with RA.[20]

MATERIALS AND METHODS

Patients

Eligible patients were male and female volunteers aged ≥ 18 years with a minimum RA disease duration of 3 months, and a minimum disease activity level of ≥ 6 swollen joints, ≥ 6 tender joints and C-reactive protein (CRP) level of ≥ 0.7 mg/dL. Patients had to be taking either MTX alone (7.5 mg $\leq$ dose ≤ 25 mg weekly) or permitted combinations of MTX plus another disease-modifying antirheumatic drug (hydroxychloroquine or chloroquine) for ≥ 3 months, and be on a stable dose of MTX for ≥ 6 weeks prior to screening. For patients on chronic topical or inhaled GCs, treatment had to be stable for ≥ 4 weeks prior to enrollment, and remain unchanged throughout the treatment period. A 6-week washout period was applied if patients had been previously treated with GCs that may have resulted in significant systemic exposure. For other RA therapies, an appropriate washout period was applied to avoid interference with interpretation of efficacy or safety endpoints. Patients were excluded if they had evidence of active or latent infection with *Mycobacterium tuberculosis*.

Study design

This was a Phase 2, international, multicenter, randomized, double-blind, parallel-group active- and placebo-controlled study in patients with RA (NCT00938587), conducted between October 2009 and July 2010. Patients were randomized 1 : 1 : 1 : 1 to receive fosdagrocorat 10 mg, fosdagrocorat 25 mg, prednisone 5 mg or placebo once daily orally for 2 weeks. Blinded treatments

were assigned in accordance with a computerized randomization list using an interactive voice response system. Considering that different tablet sizes distinguish the 10 and 25 mg doses of fosdagrocorat and that prednisone was encapsulated, patients received placebo tablets/capsules similar in appearance and size to the appropriate non-assigned treatment to maintain blinding.

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki, and the International Conference on Harmonisation Good Clinical Practice guidelines. The study protocol and informed consent documentation were reviewed and approved by the Institutional Review Boards and/or Independent Ethics Committees of each of the investigational centers.

Study endpoints

The primary efficacy endpoint was the mean change from baseline in Disease Activity Score using 28 joint counts with four variables (DAS28-4[CRP]) at week 2.[21] Secondary efficacy endpoints, assessed at weeks 1 and 2, included American College of Rheumatology (ACR) response rates for the proportion of patients achieving 20%, 50% and 70% improvement from baseline (ACR20/50/70);[22,23] mean change from baseline in ACR core components (tender and swollen joint counts [TJC, SJC]); mean change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI);[24] mean change from baseline in CRP concentration; change from baseline in Short Form-36 (SF-36) health status questionnaire, version 2;[25] change from baseline in Patient's Assessment of Arthritis Pain (PAAP); change from baseline in Physician's Global Assessment (PGA); change from baseline in Patient's Global Assessment (PtGA); mean change from baseline in DAS28-3 (DAS28 with three variables); PK of PF-00251802; oral clearance of MTX in the presence of fosdagrocorat; and plasma cortisol concentration.

Plasma analysis methodology

Blood samples for determination of plasma concentrations of PF-00251802 (active metabolite of fosdagrocorat), MTX, cortisol, fasting glucose and osteocalcin were collected at weeks 1 and 2 prior to dosing and 1, 2, 3 and 4 h after dosing for each analyte. In addition, cortisol and osteocalcin levels were analyzed at week 6, 4 weeks after the last study drug dose. Blood samples were collected prior to MTX dosing. MTX was administered at 09:00 ($\pm$1) h at the baseline visit, and at 08:00 ($\pm$1) h at all other visits. Where possible, visits were repeated at the same time for each patient. Urine samples for the bone resorption marker type 1 collagen N-telopeptide related to creatinine (uNTX-1/uCr) were collected prior to dosing at baseline and at weeks 1 and 2.

PF-00251802 concentrations were determined using a liquid chromatography/tandem mass spectrometry (LC-MS/MS) at WuXi AppTec, (Shanghai, China). The lower limit of quantification (LLOQ) for PF-00251802 was 0.100 ng/mL. The between-day assay accuracy, expressed as the ratio (%) of the estimated to the theoretical quality control (QC) concentrations, ranged from −6.7% to 1.3% for the low, medium, high and diluted QC samples. Assay precision, expressed as between-day percent coefficients of variation (%CV) of the estimated concentrations of QC samples was ≤ 10.2%. MTX concentrations were determined using high-performance LC-MS/MS (PPD, Richmond, VA, USA), and cortisol concentrations were determined using LC-MS/MS (Cephac Europe, Saint-Benoît Cedex, France). Osteocalcin and uNTX-1 concentrations were determined using enzyme-linked immunosorbent assay (ELISA). Validated analytical methods were used for these assays.

Pharmacokinetic analysis

PK of PF-00251802 following administration of fosdagrocorat tablets in patients with RA was characterized using a two-compartment population PK model with first-order elimination and first-order absorption. The analysis was performed using a nonlinear mixed effects modeling methodology in the NONMEM software system, version V level 7.2.1 (ICON Development Solutions, Ellicott City, MD, USA) and was performed to estimate the population parameter (mean and intersubject variability). Pre- or post-processing of models was conducted using R version 2.3.1®. A total of 378 PF-00251802 concentrations from 43 patients were used in the analyses. MTX PK data were also described using population PK models implemented in NONMEM, and differences in MTX oral clearance with or without co-administration of fosdagrocorat were assessed as part of the PK model.

Safety assessment

All patients who received ≥ 1 dose of study treatment were included in the safety analysis. AEs were recorded throughout the study and classified as mild, moderate or severe. Vital signs were obtained and a physical examination carried out at baseline, week 1, week 2 and at the follow-up visit 4 weeks after the last study drug dose; a 12-lead electrocardiogram was obtained at screening, baseline, week 1 and week 2.

Statistical analyses

The sample size was based on change from baseline in DAS28-4(CRP). A sample of 20 patients per treatment arm provided 90% power to detect a standardized mean difference of 1.0 between any active treatment and placebo using a one-sided *t*-test at a level of 0.05 per comparison.

The analysis set included all randomized patients who received ≥ 1 dose of the investigational drug. DAS28-4(CRP) change from baseline was analyzed using a mixed-model repeated measures (MMRM) analysis. The primary comparison was the contrast of either dose of fosdagrocorat versus placebo at week 2. Categorical variables (ACR20/50/70) were analyzed using Barnard's exact test. Continuous variables (DAS28, ACR components, etc.) were analyzed using the MMRM model with treatment group, time and treatment by time interaction as fixed effects, patients as random effect and baseline as the covariate. For plasma cortisol analysis, comparisons between groups were made using an analysis of variance model.

RESULTS

Patients

Of the 208 patients screened, 86 were randomized and received study treatment and 79 patients completed the study (Fig. 1). Patient demographics are reported in Table 1. Mean age and disease duration were generally consistent across treatment groups and the majority of patients were White in all groups. Baseline DAS28-4 (CRP), SJCs and TJCs were generally similar across treatment groups, but mean HAQ-DI scores were higher in the fosdagrocorat 10 mg (1.62) and placebo groups (1.63) compared with the fosdagrocorat 25 mg (1.47) and prednisone 5 mg groups (1.46). Across treatment groups, CRP levels ranged from 13.1 to 21.4 mg/L, and were lowest in the placebo group. The mean MTX dose was consistent across groups.

Disease activity score

At week 2, the primary efficacy time point, change from baseline in DAS28-4(CRP) for fosdagrocorat 10 and 25 mg, prednisone 5 mg and placebo was −1.69, −2.22, −1.17 and −0.96, respectively (Fig. 2). Improvement from baseline was statistically significantly greater for fosdagrocorat 10 and 25 mg compared with placebo ($P = 0.0141$ and $P < 0.0001$, respectively), and for fosdagrocorat 25 mg compared with prednisone 5 mg ($P = 0.0004$); least squares mean (LSM) change from baseline in DAS28-4(CRP) in patients treated with prednisone 5 mg was not significantly different from placebo. DAS28-3(CRP) findings were generally similar to the findings with DAS28-4(CRP) (data not shown).

ACR response rate

ACR20/50/70 response rates at weeks 1 and 2 are presented in Figure 3. At week 2, there were significantly greater ACR response rates for fosdagrocorat 25 mg
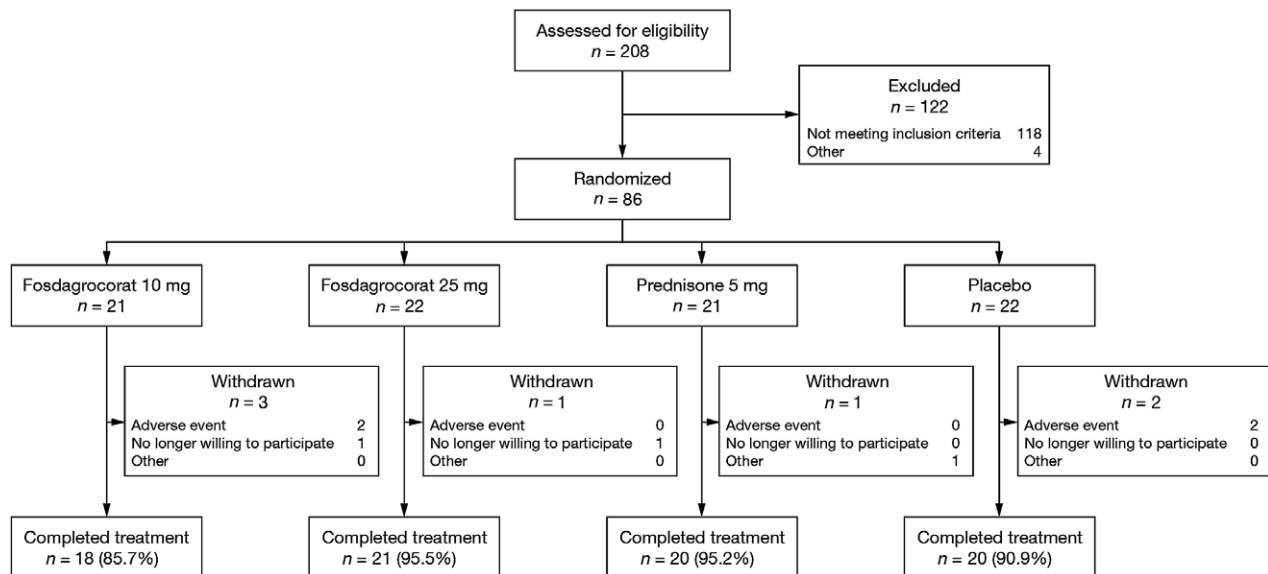

Figure 1 CONSORT diagram of patient disposition.

Table 1 Patient demographic and baseline characteristics

	Fosdagrocorat 10 mg (N = 21)	Fosdagrocorat 25 mg (N = 22)	Prednisone 5 mg (N = 21)	Placebo (N = 22)
Female, n (%)	14 (67)	12 (55)	15 (71)	20 (91)
Age, years, mean (range)	56.5 (32–77)	55.6 (33–75)	56.0 (40–77)	53.8 (29–71)
Race, n (%)				
White	21 (100)	20 (91)	19 (90)	21 (95)
Asian	0 (0)	1 (5)	2 (10)	1 (5)
Other	0 (0)	1 (5)	0 (0)	0 (0)
Disease duration, years, mean (SE)	9.27 (2.52)	7.78 (1.84)	7.61 (1.94)	8.99 (2.51)
DAS28-4(CRP), mean (SE)	6.04 (0.19)	6.14 (0.16)	5.92 (0.14)	6.03 (0.17)
Tender joint counts, mean (SE)	17.10 (1.46)	16.86 (1.15)	15.05 (0.98)	17.09 (1.28)
Swollen joint counts, mean (SE)	11.95 (1.03)	11.73 (0.86)	10.67 (0.78)	11.64 (0.87)
HAQ-DI, mean (SE)	1.62 (0.12)	1.47 (0.11)	1.46 (0.11)	1.63 (0.14)
PAAP, mean (SE)	62.45 (5.58)	60.49 (4.50)	63.17 (3.39)	66.65 (3.28)
PGA, mean (SE)	58.10 (4.35)	62.27 (2.78)	57.86 (2.90)	59.87 (3.24)
PtGA, mean (SE)	60.71 (5.30)	63.55 (4.39)	65.89 (3.26)	65.26 (3.93)
CRP, mg/L, median (IQR)	17.3 (16.7)	21.0 (17.1)	21.4 (24.0)	13.1 (9.0)
Methotrexate, mg, mean (SE)	12.98 (0.54)	12.61 (0.88)	12.98 (0.89)	13.18 (0.96)

CRP, C-reactive protein; DAS28-4, Disease Activity Score using 28 joint counts with 4 variables; HAQ-DI, Health Assessment Questionnaire Disability Index; IQR, interquartile range; N, number of patients in treatment group; n, number of patients with event; PAAP, Patient's Assessment of Arthritis Pain; PGA, Physician's Global Assessment; PtGA, Patient's Global Assessment; SE, standard error.
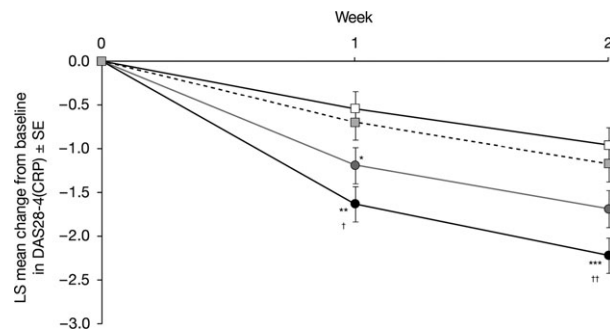

Figure 2 Least squares mean change from baseline in DAS28-4(CRP) (full analysis set). *$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$ versus placebo; †$P < 0.05$, ††$P < 0.001$ versus prednisone. CRP, C-reactive protein; DAS28-4, Disease Activity Score using 28 joint counts with four variables; LS, least squares; SE, standard error. –●–, Fosdagrocorat 10 mg; –●–, Fosdagrocorat 25 mg; -■-, Prednisone 5 mg; -□-, Placebo.

compared with placebo (ACR20: 67% *vs.* 38% [$P = 0.0442$]; ACR50: 48% *vs.* 14% [$P = 0.0117$]; ACR70: 14% *vs.* 0% [$P = 0.0442$], respectively). ACR20 and ACR50 response rates were numerically greater with fosdagrocorat 10 mg compared with placebo at week 2 (ACR20: 56% *vs.* 38%; ACR50: 22% *vs.* 14%, respectively), but these differences did not reach

statistical significance. ACR50 and ACR70 response rates were significantly greater for fosdagrocorat 25 mg compared with prednisone 5 mg at week 2 (48% *vs.* 20% [$P = 0.0347$], and 14% *vs.* 0% [$P = 0.0477$], respectively).

Physical function (HAQ-DI)

The effects of fosdagrocorat 10 and 25 mg on HAQ-DI were generally consistent with those observed for the primary endpoint (Fig. 4a; Table S1). LSM change from baseline in HAQ-DI at week 2 (Fig. 4a) was numerically greater for fosdagrocorat 10 and 25 mg compared with prednisone 5 mg and placebo (−0.40, −0.68, −0.35 and −0.23, respectively); the difference was statistically significant for fosdagrocorat 25 mg compared with both placebo ($P = 0.0013$) and prednisone 5 mg ($P = 0.0171$). There was no difference in LSM change from baseline in HAQ-DI between prednisone 5 mg and placebo.

Joint counts

At week 2, LSM change from baseline in TJC (Fig. 4b) was numerically greater for fosdagrocorat 10 and 25 mg than prednisone 5 mg and placebo, and LSM change from baseline in SJC (Fig. 4c) was numerically
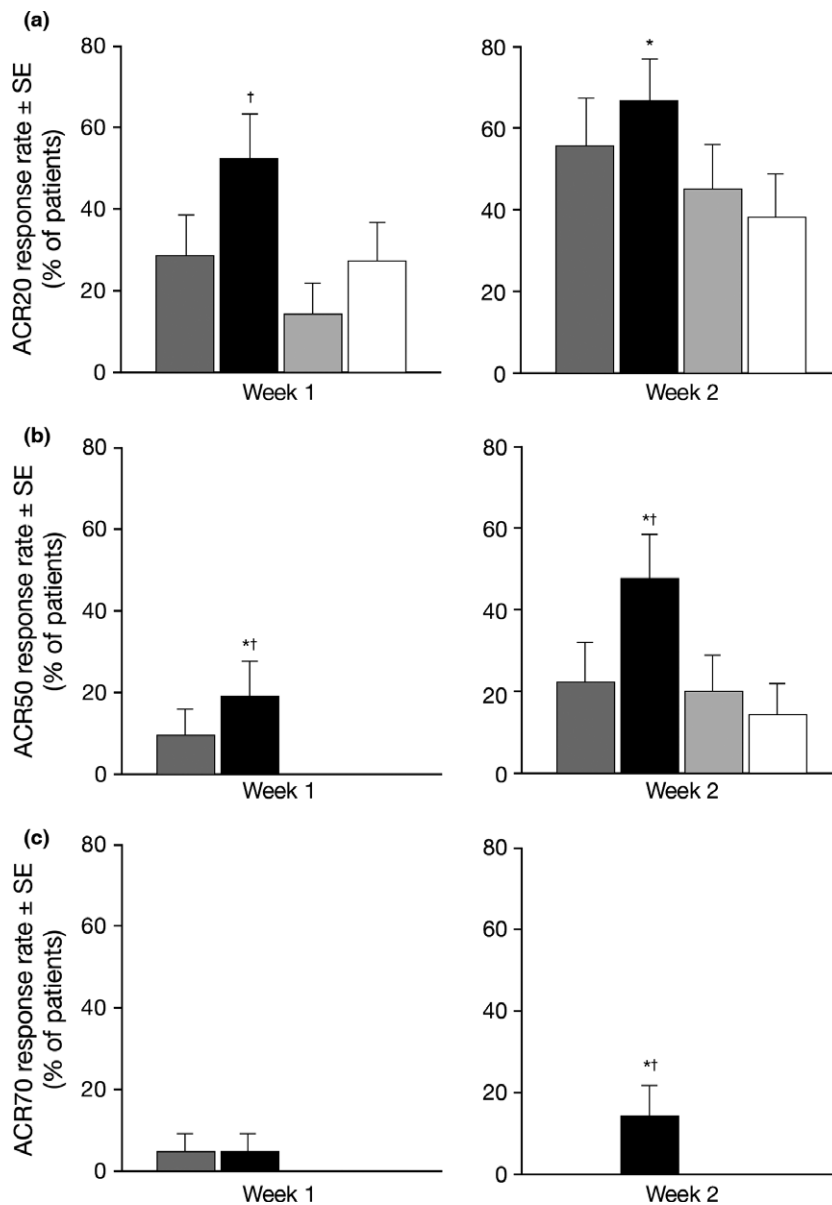
Figure 3 ACR response rates at weeks 1 and 2 for (a) ACR20, (b) ACR50 and (c) ACR70 (full analysis set). *$P < 0.05$ versus placebo; †$P < 0.05$ versus prednisone. ACR 20/50/70, American College of Rheumatology response rates for the proportion of patients achieving 20%, 50% and 70% improvement from baseline; SE, standard error. ■, Fosdagrocorat 10 mg; ■, Fosdagrocorat 25 mg; ■, Prednisone 5 mg; □, Placebo

greater in the fosdagrocorat 25 mg group compared with all other groups; these differences were not statistically significant.

CRP levels

At week 1, for fosdagrocorat 10 and 25 mg, prednisone 5 mg and placebo, LSM change from baseline in CRP levels was −14.27, −19.09, −5.80 and −1.65, respectively, and at week 2 was −18.20, −19.61, −8.52, and −4.69, respectively; reductions from baseline were clinically significant for both fosdagrocorat dose groups. Reductions in CRP from baseline were statistically significantly greater for both fosdagrocorat 10 and 25 mg compared with placebo at both week 1
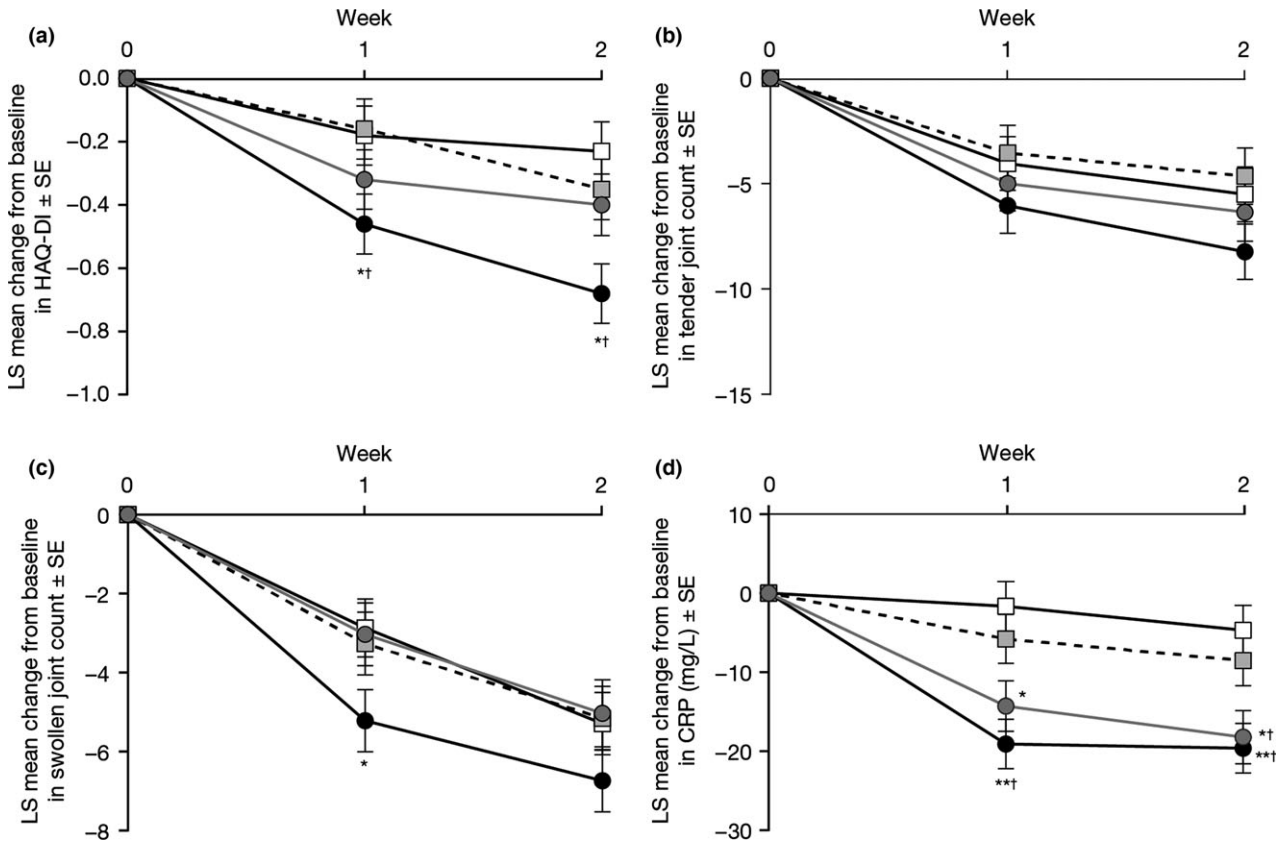
Figure 4 Least squares mean change from baseline in (a) HAQ-DI, (b) tender joint count, (c) swollen joint count and (d) CRP concentration (full analysis set). *$P < 0.05$, **$P < 0.001$ versus placebo; †$P < 0.05$ versus prednisone. CRP, C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; SE, standard error. –•–, Fosdagrocorat 10 mg; –•–, Fosdagrocorat 25 mg; -▫-, Prednisone 5 mg; –▫–, Placebo.

($P = 0.0053$ and $P < 0.0001$, respectively) and week 2 ($P = 0.0037$ and $P = 0.0009$, respectively). LSM change from baseline in CRP levels was statistically significantly greater for fosdagrocorat 25 mg compared with prednisone 5 mg at week 1 ($P = 0.0030$), and by week 2 was significantly greater for both fosdagrocorat 10 and 25 mg compared with prednisone 5 mg ($P = 0.0389$ and $P = 0.0142$, respectively). LSM change from baseline in CRP levels for prednisone 5 mg was greater than for placebo at both weeks 1 and 2, although these differences were not clinically or statistically significant.

Patient-reported outcomes

There were no significant differences between groups in the physical or mental component summary scores of the SF-36. At week 2, fosdagrocorat 25 mg showed a significantly greater improvement in the LSM change from baseline in bodily pain over placebo (11.92 *vs.*

5.13; $P = 0.0190$); all other domains were not significantly different between fosdagrocorat and placebo. There were no significant differences in SF-36 domain scores between fosdagrocorat 10 mg and placebo, or between either fosdagrocorat dose and prednisone 5 mg. LSM improvements from baseline in PAAP, PGA and PtGA at week 2 were significantly greater for fosdagrocorat 25 mg compared with placebo (PAAP, −28.73 *vs.* −12.84, $P = 0.0271$; PGA, −31.27 *vs.* −14.27, $P = 0.0018$; PtGA, −28.64 *vs.* −11.12, $P = 0.0138$). There were no significant differences in LSM change from baseline in PAAP, PGA or PtGA between fosdagrocorat 10 mg and placebo, or between either fosdagrocorat dose and prednisone 5 mg.

PK and MTX interactions

Population PK modeling of PF-00251802 (active metabolite of fosdagrocorat) indicated a dose-

Table 2 Summary of adverse events

	Fosdagrocorat 10 mg (N = 21)	Fosdagrocorat 25 mg (N = 22)	Prednisone 5 mg (N = 21)	Placebo (N = 22)
AEs, n (%)				
Patients with AE	8 (38.1)	3 (13.6)	4 (19.0)	12 (54.5)
Patients with serious AEs	0	0	0	0
Patients with severe AEs	1 (4.8)	0	0	0
Discontinuations due to AEs	2 (9.5)	0	0	2 (9.1)
Most common AEs, n (%)[†]				
Upper respiratory tract infection	2 (9.5)	0	0	0
Nasopharyngitis	1 (4.8)	0	2 (9.5)	0
Headache	0	0	2 (9.5)	4 (18.2)
Arthralgia	0	0	1 (4.8)	2 (9.1)
Rheumatoid arthritis	0	0	0	2 (9.1)
Disturbance in attention	0	0	0	2 (9.1)
Rash	0	0	0	2 (9.1)

[†]Reported in ≥ 2 patients in any group. AE, adverse event; N, number of patients in treatment group; n, number of patients with event.

proportional increase in PF-00251802 exposure, and an estimated mean terminal half-life of 35 h in patients with RA. Mean (standard error) PF-00251802 oral clearance in patients with RA in this study was estimated to be 4.74 (0.22) L/h.

MTX oral clearance values prior to dosing on day 1 and on day 14 of fosdagrocorat administration were similar in all treatment groups, indicating that fosdagrocorat does not have a clinically relevant effect on MTX exposure in patients with RA (data not shown).

Plasma cortisol level

At baseline, 0 h, mean cortisol levels (ng/mL) were similar across treatment groups (fosdagrocorat 10 mg, 106.85; fosdagrocorat 25 mg, 110.50; prednisone 5 mg, 106.38; placebo, 105.14). Both doses of fosdagrocorat were associated with near-complete suppression of adrenal secretion of cortisol (Fig. S1). At week 1, 0 h, mean cortisol levels for PF-04171327 10 and 25 mg, prednisone 5 mg and placebo were 14.65, 6.09, 111.63 and 113.06 ng/mL, respectively, and at week 2, 0 h, were 14.70, 4.99, 90.44, and 112.62 ng/mL, respectively. The differences in cortisol suppression between fosdagrocorat doses and both placebo and prednisone 5 mg were highly significant at both weeks 1 and 2 (all $P < 0.001$). At week 6, 4 weeks after the last study drug dose, absolute plasma cortisol levels had returned to baseline values for patients treated with both fosdagrocorat 10 and 25 mg (117.74 and 100.59 ng/mL, respectively; Fig. S1).

Bone biomarker levels

Mean osteocalcin levels and mean uNTX-1/uCr values are presented in Figure S2, and were broadly similar between both fosdagrocorat doses and placebo; however, the data were highly variable.

Safety

A total of 69 AEs were reported in 27 (31.4%) patients: 15 AEs in eight (38.1%) patients in the PF-04171327 10 mg group, six AEs in three (13.6%) patients in the fosdagrocorat 25 mg group, 11 AEs in four (19.0%) patients in the prednisone 5 mg group and 37 AEs in 12 (54.5%) patients in the placebo group (Table 2). The majority of AEs were mild in severity (50 [72%] mild, 17 [25%] moderate and two [3%] severe). Moderate AEs occurred in similar numbers of patients in the fosdagrocorat and placebo groups. One patient (fosdagrocorat 10 mg group) had two AEs that were severe (asthenia and viral infection), and four patients discontinued the study due to an AE (fosdagrocorat 10 mg, n = 2; placebo, n = 2). There were no serious AEs during the study. The most common AE was headache, which occurred in two patients in the prednisone 5 mg group and four patients in the placebo group. No other AEs occurred in more than two patients in any group. No patients reported an AE of Cushingoid appearance. No patients met criteria for abnormal electrolyte values. Mean blood pressure (diastolic and systolic) and mean fasting glucose levels

over time are presented in Table S2 and Figure S3, respectively. Fasting glucose appeared to be generally unchanged from baseline in the placebo group at weeks 1 and 2, and was slightly decreased in all active-treatment groups.

DISCUSSION

This Phase 2 study was designed to assess the efficacy and safety of fosdagrocorat, a novel potential DAGR, in patients with active RA and an inadequate response to MTX. Fosdagrocorat demonstrated strong efficacy and rapid onset of action in improving RA signs and symptoms as measured by the primary endpoint, change from baseline to week 2 in DAS28-4(CRP) for fosdagrocorat 10 and 25 mg relative to placebo and prednisone 5 mg. The clinical efficacy of fosdagrocorat was supported by evaluation of the secondary endpoints, including ACR responses and ACR core component scores, including HAQ-DI. The profound anti-inflammatory effect of fosdagrocorat was also demonstrated by the rapid and sustained reduction in CRP, an objective marker of inflammation.

In terms of safety, both fosdagrocorat 10 and 25 mg were associated with manageable tolerability in this 2-week study. Although complete suppression of plasma cortisol was seen with both doses of fosdagrocorat, no patient demonstrated clear symptoms of either GC excess or adrenal insufficiency in this study. Plasma cortisol levels had returned to baseline values within 4 weeks after the last study drug dose, indicating that fosdagrocorat does not cause lasting suppression of cortisol levels after 2 weeks of treatment. However, more careful monitoring of hypothalamic-pituitary-adrenal axis function and time to recovery will need to be considered in future studies with longer treatment duration.

The use of GCs to treat RA is well established,[1–3] despite their association with significant side effects. This study has demonstrated robust anti-inflammatory activity with a partial GR agonist that shows evidence of dissociation. It was hypothesized that a synthetic GR ligand with the efficacy of GC, but without the accompanying side effects, would meet an unmet medical need for the treatment of inflammatory diseases. Fosdagrocorat has key structural components of prednisolone and the GR antagonist RU-486, combined into a non-steroidal scaffold, to create a high-affinity and selective GR ligand that manifests both partial agonist activity for inflammatory cytokine inhibition and full antagonist activity in cellular assays.[26] In mesenchymal stem cells and human primary cells, fosdagrocorat displays mostly antagonistic effects on a number of GR-regulated functions (e.g., osteoblastogenesis and adipogenesis), while displaying partial agonist effects on other GR-regulated functions (e.g., bone matrix formation and gluconeogenesis).[26] Dissociation was demonstrated in mouse models in which fosdagrocorat conferred comparable anti-inflammatory activity to prednisolone, but reduced side effects against biomarkers of osteoporosis and diabetes.[26] In this study, fosdagrocorat was more efficacious than prednisone 5 mg in reducing the signs and symptoms of RA. At higher doses (10–60 mg), treatment with prednisolone (active metabolite of prednisone) can produce a similar improvement from baseline in DAS28 score to that seen with fosdagrocorat in this study, and leads to a reduction in inflammatory biomarkers.[27,28] However, in this dose range prednisolone also causes substantial decreases in the bone markers osteocalcin and procollagen type 1 N-terminal propeptide, prohibiting the long-term use of prednisone for chronic diseases such as RA.[27] The potential exists for fosdagrocorat to achieve greater efficacy than low-dose prednisone in RA, while at the same time keeping the risk of GC-related AEs at an acceptable level.

The main aim of this study was to assess the anti-inflammatory efficacy of fosdagrocorat, and not to make a rigorous assessment of biomarker responses. Observations of some biomarkers were recorded (the bone formation marker, osteocalcin; the bone resorption marker, uNTX-1; neutrophil stimulation; eosinophil suppression; and serum glucose levels); however, data on these biomarkers were exploratory and gathered over a short time-interval with no control for patient baseline characteristics that could influence these parameters. Consequently, the results were highly variable and do not offer clear evidence as to whether fosdagrocorat provides dissociation between anti-inflammatory effects in RA and many of the adverse effects seen with current GC therapies.

Further studies of longer duration are required to confirm the initial results presented here. A 12-week, Phase 2, randomized double-blind study (NCT01393639) has recently evaluated the efficacy and safety of fosdagrocorat versus prednisone or placebo in patients with RA and publication of the findings is awaited with interest.

In conclusion, this study has demonstrated the efficacy and safety of the potential DAGR fosdagrocorat in patients with RA compared with both prednisone and placebo. These results support ongoing evaluation of fosdagrocorat as a potential treatment for RA, including long-term follow-up of AEs and clinical outcomes.

DISCLOSURES

Thomas Stock, Dona Fleishaker, Arnab Mukherjee and Charles Mebus are employees and shareholders of Pfizer Inc. Xin Wang was an employee and shareholder of Pfizer Inc at the time of the study.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study/analyses and data acquisition. Xin Wang planned and performed the statistical analyses. All authors were involved in the data interpretation, and manuscript reviewing and development.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1 Pre-dose mean cortisol values at baseline (week 0), week 1, week 2 and week 6 (4 weeks after last study drug dose). SD, standard deviation.

Figure S2 (a) Pre-dose mean osteocalcin values at baseline (week 0), week 1, week 2 and week 6 (4 weeks after last study drug dose) and (b) mean uNTX-1/uCr at baseline (week 0), week 1 and week 2. BCE, bone collagen equivalents; CR, creatinine; SD, standard deviation; uCr, urinary creatinine; uNTX-1, urinary N-telopeptide of type 1 collagen.

Figure S3 Pre-dose mean fasting glucose values at baseline (week 0), week 1, week 2 and week 6 (4 weeks after last study drug dose). SD, standard deviation.

Table S1 ACR core component scores at baseline and Week 2 (full analysis set). ACR, American College of Rheumatology; HAQ-DI, Health Assessment Questionnaire Disability Index; SE, standard error.

Table S2 Pre-dose mean diastolic and systolic blood pressure at baseline (Week 0), and change from baseline at Week 1, Week 2 and Week 6 (4 weeks after last study drug dose). SD, standard deviation.