**Fosdagrocorat (PF-04171327) versus prednisone or placebo in rheumatoid arthritis: a randomised, double-blind, multicentre, Phase 2b study**

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**ONLINE SUPPLEMENTARY MATERIAL**

**Online supplementary section S1** Exclusion criteria

Patients presenting with any of the following were not included in the study:

1. Diagnosis of any other arthritides (inflammatory or non-inflammatory) or chronic pain condition (fibromyalgia, neuropathy) that, in the opinion of the investigator, could have interfered with disease activity assessments.
2. Severe, progressive, or uncontrolled renal, hepatic, haematologic, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurologic disease, or any other conditions, which made the patient unsuitable for the study.
3. Any lymphoproliferative disorder, such as Epstein Barr virus, history of lymphoma, leukaemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease.
4. A prior history of malignancy, excluding patients with non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma *in situ*, who were eligible immediately after adequate treatment.
5. Blood dyscrasias including confirmed:

* Haemoglobin <9 g/dL or haematocrit <30%;
* Absolute white blood cell count <3.0 × 109/L;
* Absolute neutrophil count <1.2 × 109/L;
* Platelet count <100 × 109/L.

1. Patients treated with the following therapies and who did not observe the required wash-out period before baseline (Day 0) period:

**Seven days or five half-lives (whichever is longer)**:

* Cytochrome P450 3A4 (CYP3A4) inducers or inhibitors.

**Four weeks:**

* Experimental non-steroidal anti-inflammatory drugs (NSAIDs) − any experimental non-selective NSAID or experimental selective NSAID (e.g., COX-2 inhibitor).
* Other − herbal medications, immunization with any live or live attenuated virus vaccination.

**Six weeks:**

* Glucocorticoids (GCs) by any route (oral, intra-articular, intramuscular, or intravenous) that may result in significant systemic exposure.

**Biologic disease-modifying antirheumatic drugs (DMARDs):**

* **Four weeks**: Anakinra and etanercept.
* **Six weeks**: Adalimumab.
* **Ten weeks**: Infliximab.
* **Ten weeks**: Golimumab.
* **Twelve weeks**: Abatacept, tocilizumab, and certolizumab pegol.
* **Twelve months**: Rituximab or other selective B-lymphocyte depleting agents; however, a B-lymphocyte count is recommended to consider the patient sufficiently washed out before treatment with study drug.

**Other DMARDs:**

**Four weeks:**

* D-penicillamine, azathioprine, cyclosporine, tacrolimus, and staphylococcal protein.
* Immuno-absorbent pheresis columns.
* Tetracyclines, unless prescribed for the treatment of acne or other dermatologic disorders.

**Eight weeks:**

* Auranofin (oral gold), aurothioglucose (injectable gold), aurothiomalate (injectable gold).
* Leflunomide.
* Note: In addition to a washout period of 8 weeks for leflunomide, 1 of the following elimination procedures must have been adhered to for a minimum of 14 days: cholestyramine at a dose of 8 g, 3 times daily for at least 24 hours, or activated powdered charcoal at a dosage of 50 g, 4 times daily for at least 24 hours.

1. Participation in studies of investigational compounds within 4 weeks or 5 half-lives (whichever was longer) prior to the first dose of study drug. Patients could not participate in other clinical studies at any time during their participation in this study. Patients were to discuss any prior exposure to an investigational biologic(s) with the Pfizer Medical Monitor.
2. Hepatic enzyme elevations (alanine aminotransferase or alkaline phosphatase) >1.3 upper limit of normal confirmed at the screening visit.
3. Diagnosis of insulin-dependent diabetes mellitus or poorly controlled non-insulin-dependent diabetes mellitus (glycosylated haemoglobin value of >8.0% [American Diabetes Association recommendation of poorly controlled]).
4. Drug or alcohol abuse with less than 6 months of continued abstinence prior to the screening visit.
5. Clinically significant infections (those requiring hospitalization or requiring parenteral antimicrobial therapy) within 6 months of the screening visit.
6. A body temperature of 38ºC/100.4ºF or higher at the baseline visit or a febrile illness within 14 days prior to the first dose.
7. An infection with human immunodeficiency virus or Hepatitis B or C.
8. Any condition possibly affecting oral drug absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy).
9. Significant trauma, blood loss, or major surgery (involving anaesthesia or respiratory assistance within 4 weeks of the screening visit).
10. Bone fracture and/or immobility/immobilization within 3 months of the screening visit.
11. A standard 12-lead electrocardiograph (ECG) demonstrating a QTcF >450 ms for males and QTcF >480 ms for females or other clinically significant abnormality at the screening visit. If the QTcF was greater than 450 ms (for males) or 480 ms (for females), the ECG was to be repeated two more times and the average of the three QTcF values were to be used to determine the patient’s eligibility.
12. Blood donation of approximately 1 pint (500 mL) within 60 days of the screening visit.
13. Patients with a previous or current history of glaucoma or ocular herpetic infections.
14. Patients known to be GC “non-responders” or with a previous history of intolerance or significant adverse effects with GC therapy.
15. Documented history of peptic ulcer disease within 5 years.
16. Ongoing treatment with an NSAID or selective COX-2 inhibitor that was not stable (dose and duration) for at least 6 weeks prior to screening.
17. Female patients who were pregnant or lactating.
18. Current household contact with children who had received varicella or oral polio vaccine within 8 weeks of the screening visit.
19. Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that could increase the risk associated with study participation or investigational product administration, or could interfere with the interpretation of study results and, in the judgement of the investigator, would have made the patient inappropriate for entry into this study.

**Online supplementary section S2**Countries where study was conducted

Patients were recruited at 73 centres in Bulgaria, Colombia, Czech Republic, Germany, Hungary, India, Republic of Korea, Malaysia, Mexico, Poland, Romania, Russian Federation, Serbia, Slovakia, Spain, Ukraine, and the USA.

**Online supplementary section S3** Hypothalamic-pituitary-adrenal axis recovery assessment

A standard adrenocorticotropic hormone (ACTH) stimulation test was used to assess the hypothalamic-pituitary-adrenal axis recovery. ACTH stimulation was to be carried out in the morning (before 10 AM), preferably after an overnight fast. Using tuberculin syringe or intravenous, 250 μg ACTH was administered intramuscularly over a 2-minute period or per pharmacy instructions. Blood samples for cortisol were collected at 30 minutes and 60 minutes after the injection using the correct collection tubes.

**Online supplementary section S4** Further details for a patient who died after study completion

The patient was a 39-year-old white female who was randomised to fosdagrocorat 5 mg once daily. Approximately 6 months after the last dose of study drug, the patient was diagnosed with glioblastoma. The patient underwent surgery, radiotherapy, and chemotherapy but died as a result of the glioblastoma 1 year after diagnosis (approximately 18 months after study completion). The investigator considered that there was not a reasonable possibility that the glioblastoma was related to study drug, a concomitant drug, or to the clinical study procedure.

**Online supplementary table S1** Number of patients randomised per study site and country

|  |  |  |
| --- | --- | --- |
| **Country** | **Study site** | **Number of patients randomised** |
| Bulgaria | 1080 | 4 |
| 1083 | 2 |
| 1084 | 3 |
| 1104 | 1 |
| Colombia | 1054 | 2 |
| 1055 | 1 |
| 1057 | 5 |
| 1058 | 7 |
| Czech Republic | 1110 | 2 |
| 1111 | 2 |
| 1114 | 1 |
| Germany | 1034 | 1 |
| 1053 | 1 |
| 1141 | 2 |
| Hungary | 1009 | 3 |
| 1010 | 7 |
| 1012 | 1 |
| 1013 | 8 |
| 1123 | 9 |
| India | 1021 | 2 |
| 1022 | 1 |
| 1023 | 1 |
| Republic of Korea | 1059 | 11 |
| 1060 | 2 |
| 1061 | 1 |
| 1063 | 4 |
| Malaysia | 1069 | 2 |
| 1070 | 1 |
| Mexico | 1088 | 3 |
| 1089 | 32 |
| 1125 | 8 |
| Poland | 1019 | 1 |
| 1122 | 2 |
| Romania | 1066 | 1 |
| 1067 | 3 |
| 1152 | 4 |
| Russian Federation | 1038 | 9 |
| 1040 | 27 |
| 1041 | 13 |
| 1042 | 2 |
| 1043 | 4 |
| 1044 | 2 |
| 1045 | 4 |
| 1046 | 3 |
| 1048 | 4 |
| 1050 | 7 |
| 1097 | 8 |
| 1116 | 1 |
| 1153 | 1 |
| 1154 | 6 |
| 1155 | 1 |
| Serbia | 1117 | 1 |
| 1118 | 3 |
| Slovakia | 1100 | 8 |
| 1101 | 2 |
| 1102 | 8 |
| 1103 | 1 |
| 1167 | 4 |
| Spain | 1098 | 6 |
| 1157 | 1 |
| Ukraine | 1074 | 11 |
| 1075 | 12 |
| 1076 | 1 |
| 1077 | 1 |
| 1085 | 5 |
| 1159 | 3 |
| 1164 | 2 |
| 1166 | 5 |
| United States | 1016 | 4 |
| 1072 | 5 |
| 1131 | 5 |
| 1136 | 1 |
| 1139 | 1 |
| **Total** |  | **323** |

**Online supplementary table S2** Baseline and LS mean change from baseline in HAQ-DI and SF-36 scores at Week 8

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Fosdagrocorat  1 mg** | **Fosdagrocorat  5 mg** | **Fosdagrocorat 10 mg** | **Fosdagrocorat 15 mg** | **Prednisone  5 mg** | **Prednisone 10 mg** | **Placebo** |
| *HAQ-DI* |  |  |  |  |  |  |  |
| Mean (SD) baseline | 1.40 (0.71) | 1.60 (0.64) | 1·47 (0.60) | 1.61 (0.63) | 1.62 (0.55) | 1.63 (0.58) | 1.65 (0.56) |
| LS mean (SE) change from baseline | –0.26 (0.08) | –0.59 (0.08) | –0.60 (0.08) | –0.55 (0.08) | –0.50 (0.08) | –0.77 (0.08) | –0.19 (0.08) |
| *SF-36 PCS* |  |  |  |  |  |  |  |
| Mean (SD) baseline | 33.24 (7.29) | 31.49 (6.21) | 30.44 (6.53) | 31.87 (7.41) | 31.86 (6.46) | 30.52 (7.18) | 31.68 (6.08) |
| LS mean (SE) change from baseline | 5.24 (1.03) | 7.85 (1.04) | 9.65 (1.03) | 7.15 (1.02) | 7.06 (1.03) | 9.62 (1.03) | 3.45 (1.03) |
| *SF-36 MCS* |  |  |  |  |  |  |  |
| Mean (SD) baseline | 38.28 (10.34) | 38.08 (10.62) | 42.41 (12.08) | 37.61 (10.79) | 40.05 (11.55) | 37.30 (10.07) | 38.74 (9.56) |
| LS mean (SE) change from baseline | 2.57 (1.39) | 6.07 (1.41) | 6.03 (1.40) | 6.47 (1.39) | 5.30 (1.40) | 8.76 (1.40) | 4.58 (1.39) |

All study treatments were administered once daily.

HAQ-DI, Health Assessment Questionnaire-Disability Index; LS, least squares; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SE, standard error; SF-36, 36-item short form health survey.

**Online supplementary table S3** Mean percent change from baseline in bone biomarkers osteocalcin and CTx at Week 8 (FAS, longitudinal model), comparisons with placebo, prednisone 5 mg and prednisone 10 mg

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  | **Treatment difference (95% CI) at Week 8 (0 hour)** | | |
|  |  |  |  | **Primary comparison** |  |
| **Treatment group** | **N** | **LS mean (SE) at Week 8** | **Fosdagrocorat vs placebo** | **Fosdagrocorat vs prednisone  5 mg** | **Fosdagrocorat vsprednisone 10 mg** |
| *OC* |  |  |  |  |  |
| Fosdagrocorat 1 mg | 44 | –0.52 (3.77) | –8.84 (–19.36, 1.68) | 5.57 (–4.96, 16.10) | 19.49 (9.00, 29.99) |
| Fosdagrocorat 5 mg | 42 | –10.79 (3.80) | –19.10 (–29.68, –8.53) | –4.70 (–15.27, 5.87) | 9.22 (–1.30, 19.75) |
| Fosdagrocorat 10 mg | 44 | –11.69 (3.75) | –20.01 (–30.53, –9.48) | –5.60 (–16.11, 4.91) | 8.32 (–2.13, 18.77) |
| Fosdagrocorat 15 mg | 43 | –15.52 (3.81) | –23.83 (–34.45, –13.21) | –9.42 (–20.00, 1.16) | 4.50 (–6.00, 15.00) |
| Prednisone 5 mg | 43 | –6.09 (3.80) | – | – | – |
| Prednisone 10 mg | 44 | –20.02 (3.76) | – | – | – |
| Placebo | 41 | 8.31 (3.81) | – | – | – |
| *CTx* |  |  |  |  |  |
| Fosdagrocorat 1 mg | 44 | 10.60 (6.94) | –6.86 (–26.29, 12.56) | 10.06 (–9.37, 29.49) | 13.00 (–6.37, 32.38) |
| Fosdagrocorat 5 mg | 42 | –3.64 (6.99) | –21.09 (–40.59, –1.59) | –4.17 (–23.67, 15.33) | –1.23 (–20.65, 18.19) |
| Fosdagrocorat 10 mg | 44 | 9.27 (6.94) | –8.18 (–27.67, 11.31) | 8.73 (–10.75, 28.22) | 11.68 (–7.64, 31.00) |
| Fosdagrocorat 15 mg | 43 | 15.10 (6.96) | –2.35 (–21·86, 17.15) | 14.57 (–4.93, 34.07) | 17.51 (–1.84, 36.86) |
| Prednisone 5 mg | 43 | 0.54 (7.02) | – | – | – |
| Prednisone 10 mg | 44 | –2.41 (6.94) | – | – | – |
| Placebo | 41 | 17.46 (7.02) | – | – | – |

All study treatments were administered once daily.  
All statistics are derived from a longitudinal mixed model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value.

CI, confidence interval; CTx, C-terminal telopeptide; FAS, full analysis set; LS, least squares; N, number of patients with observations;   
OC, osteocalcin; SE, standard error.

**Online supplementary table S4** Treatment-emergent adverse events (all cause)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number (%) of subjects experiencing event** | | | | | | |
|  | **Fosdagrocorat** | | | | **Prednisone** | |  |
| **System organ class term** | **1 mg** | **5 mg** | **10 mg** | **15 mg** | **5 mg** | **10 mg** | **Placebo** |
| Subjects evaluable for AEs | 45 | 47 | 45 | 48 | 45 | 46 | 47 |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 2 (4.4) | 0 | 0 | 0 | 1 (2.2) | 0 | 1 (2.1) |
| Anaemia | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Eosinophilia | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Monocytosis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Neutropenia | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| CARDIAC DISORDERS | 0 | 1 (2.1) | 1 (2.2) | 0 | 1 (2.2) | 0 | 1 (2.1) |
| Bradycardia | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Extrasystoles | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Sinus bradycardia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Sinus tachycardia | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Coronary artery disease | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| ENDOCRINE DISORDERS | 0 | 1 (2.1) | 0 | 0 | 1 (2.2) | 0 | 0 |
| Adrenal insufficiency | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Goiter | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| EYE DISORDERS | 1 (2.2) | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Cataract | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Dry eye | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Astigmatism | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Presbyopia | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Visual impairment | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | 2 (4.4) | 2 (4.3) | 3 (6.7) | 3 (6.3) | 5 (11.1) | 3 (6.5) | 3 (6.4) |
| Food poisoning | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Gastritis | 0 | 1 (2.1) | 0 | 1 (2.1) | 0 | 0 | 0 |
| Diarrhoea | 1 (2.2) | 0 | 0 | 2 (4.2) | 2 (4.4) | 2 (4.3) | 0 |
| Gastroesophageal reflux disease | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Abdominal discomfort | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Abdominal pain | 0 | 0 | 2 (4.4) | 0 | 1 (2.2) | 0 | 0 |
| Abdominal pain upper | 1 (2.2) | 0 | 0 | 1 (2.1) | 1 (2.2) | 0 | 1 (2.1) |
| Nausea | 0 | 0 | 0 | 0 | 2 (4.4) | 0 | 1 (2.1) |
| Vomiting | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 1 (2.1) |
| Aphthous stomatitis | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Oral discomfort | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 4 (8.9) | 1 (2.1) | 2 (4.4) | 3 (6.3) | 2 (4.4) | 4 (8.7) | 1 (2.1) |
| Pyrexia | 0 | 0 | 1 (2.2) | 1 (2.1) | 0 | 2 (4.3) | 0 |
| Chest pain | 0 | 0 | 0 | 1 (2.1) | 1 (2.2) | 0 | 0 |
| Chills | 1 (2.2) | 0 | 1 (2.2) | 1 (2.1) | 0 | 2 (4.3) | 0 |
| Face oedema | 1 (2.2) | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Fatigue | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Feeling hot | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Local swelling | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Drug ineffective | 1 (2.2) | 1 (2.1) | 0 | 0 | 0 | 1 (2.2) | 1 (2.1) |
| HEPATOBILIARY DISORDERS | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Hepatic steatosis | 0 | 0 | 1 (2·2) | 0 | 0 | 0 | 0 |
| INFECTIONS AND INFESTATIONS | 6 (13.3) | 7 (14.9) | 10 (22.2) | 6 (12.5) | 5 (11.1) | 5 (10.9) | 6 (12.8) |
| Abscess bacterial | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Pharyngitis bacterial | 1 (2.2) | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Candida infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Bronchitis | 0 | 1 (2.1) | 1 (2.2) | 0 | 1 (2·2) | 0 | 1 (2.1) |
| Cholecystitis infective | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Cystitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Gastroenteritis | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Gingivitis | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 1 (2.2) | 3 (6.4) | 3 (6.7) | 2 (4.2) | 0 | 1 (2.2) | 1 (2.1) |
| Pharyngitis | 1 (2.2) | 0 | 0 | 0 | 1 (2.2) | 0 | 1 (2.1) |
| Respiratory tract infection | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Rhinitis | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Sinusitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Upper respiratory tract infection | 1 (2.2) | 0 | 3 (6.7) | 2 (4.2) | 0 | 0 | 1 (2.1) |
| Urinary tract infection | 0 | 0 | 1 (2.2) | 0 | 0 | 1 (2.2) | 0 |
| Herpes virus infection | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Influenza | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.2) | 0 |
| Oral herpes | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Respiratory tract infection viral | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Viral infection | 1 (2.2) | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Viral rhinitis | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.2) | 0 |
| Viral upper respiratory tract infection | 0 | 1 (2.1) | 1 (2.2) | 0 | 0 | 1 (2.2) | 0 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 1 (2.2) | 1 (2.1) | 1 (2.2) | 1 (2.1) | 1 (2.2) | 1 (2.2) | 0 |
| Spinal compression fracture | 0 | 1 (2.1) | 1 (2.2) | 0 | 0 | 0 | 0 |
| Contusion | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Fall | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Ligament sprain | 1 (2.2) | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Soft tissue injury | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| INVESTIGATIONS | 2 (4.4) | 1 (2.1) | 6 (13.3) | 2 (4.2) | 2 (4.4) | 6 (13.0) | 3 (6.4) |
| Blood pressure increased | 0 | 0 | 1 (2.2) | 0 | 1 (2.2) | 1 (2.2) | 0 |
| Blood creatine phosphokinase increased | 0 | 0 | 1 (2.2) | 1 (2.1) | 0 | 0 | 0 |
| Alanine aminotransferase increased | 2 (4.4) | 1 (2.1) | 4 (8.9) | 0 | 0 | 3 (6.5) | 3 (6.4) |
| Aspartate aminotransferase increased | 1 (2.2) | 1 (2.1) | 1 (2.) | 0 | 0 | 2 (4.3) | 0 |
| Blood bilirubin increased | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Gamma, glutamyltransferase increased | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Body temperature increased | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Weight increased | 0 | 0 | 0 | 1 (2.1) | 1 (2.2) | 0 | 0 |
| Blood creatinine decreased | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| METABOLISM AND NUTRITION DISORDERS | 1 (2.2) | 0 | 2 (4.4) | 2 (4.2) | 0 | 2 (4.3) | 1 (2.1) |
| Decreased appetite | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Dehydration | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Polydipsia | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Dyslipidaemia | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.1) |
| Hypercholesterolemia | 0 | 0 | 1 (2.2) | 1 (2.1) | 0 | 0 | 0 |
| Hyperuricemia | 1 (2.2) | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 3 (6.7) | 3 (6.4) | 7 (15.6) | 3 (6.3) | 5 (11.1) | 9 (19.6) | 3 (6.4) |
| Pathological fracture | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Arthralgia | 1 (2.2) | 1 (2.1) | 1 (2.2) | 0 | 1 (2.2) | 5 (10.9) | 0 |
| Arthritis | 1 (2.2) | 0 | 3 (6.7) | 1 (2.1) | 0 | 0 | 1 (2.1) |
| Arthropathy | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Joint swelling | 0 | 0 | 0 | 0 | 1 (2.2) | 2 (4.3) | 0 |
| Rheumatoid arthritis | 1 (2.2) | 0 | 0 | 2 (4.2) | 3 (6.7) | 1 (2.2) | 1 (2.1) |
| Rheumatoid nodule | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Muscle spasms | 0 | 0 | 2 (4.4) | 0 | 0 | 1 (2.2) | 0 |
| Intervertebral disc protrusion | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Back pain | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.2) | 0 |
| Muscle contracture | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Pain in extremity | 0 | 1 (2.1) | 0 | 0 | 1 (2.2) | 1 (2.2) | 1 (2.1) |
| Synovial cyst | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Tendonitis | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS) | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Glioblastoma | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| NERVOUS SYSTEM DISORDERS | 2 (4.4) | 0 | 1 (2.2) | 3 (6.3) | 0 | 5 (10.9) | 1 (2.1) |
| Headache | 1 (2.2) | 0 | 0 | 1 (2.1) | 0 | 4 (8.7) | 0 |
| Migraine | 1 (2.2) | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Tremor | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Dizziness | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Paraesthesia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Presyncope | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Sciatica | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| PSYCHIATRIC DISORDERS | 0 | 2 (4.3) | 0 | 0 | 1 (2.2) | 0 | 0 |
| Depression | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Insomnia | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Sleep disorder | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| RENAL AND URINARY DISORDERS | 0 | 0 | 2 (4.4) | 0 | 0 | 1 (2.2) | 0 |
| Microalbuminuria | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Nocturia | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Nephrolithiasis | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7)\* |
| Polymenorrhea | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.7)\* |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 1 (2.2) | 0 | 1 (2.2) | 1 (2.) | 1 (2.2) | 1 (2.2) | 1 (2.1) |
| Asthma | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Chronic obstructive pulmonary disease | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Oropharyngeal pain | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Productive cough | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 0 |
| Respiratory disorder | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.1) |
| Epistaxis | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 0 | 1 (2.1) | 1 (2.2) | 1 (2.1) | 0 | 1 (2.2) | 0 |
| Dermal cyst | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Dry skin | 0 | 1 (2.1) | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 0 | 0 | 1 (2.2) | 0 | 0 | 0 | 0 |
| Rash | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| SURGICAL AND MEDICAL PROCEDURES | 1 (2.2) | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Knee operation | 1 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Tooth extraction | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| VASCULAR DISORDERS | 0 | 4 (8.5) | 1 (2.2) | 3 (6.3) | 1 (2.2) | 2 (4.3) | 0 |
| Hypotension | 0 | 1 (2.1) | 1 (2.2) | 1 (2.1) | 0 | 0 | 0 |
| Flushing | 0 | 0 | 0 | 1 (2.1) | 0 | 0 | 0 |
| Hot flush | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |
| Hypertension | 0 | 3 (6.4) | 0 | 1 (2.1) | 1 (2.2) | 0 | 0 |
| Varicose vein | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 |

All study treatments were administered once daily.

Except for the number of AEs, patients were counted only once per treatment in each row. MedDRA (v17.0) coding dictionary applied.

\*Denominator based on number of female subjects for the event.

AE, adverse events; FAS, full analysis set.

**Online supplementary figure S1** Mechanism of action of fosdagrocorat versus prednisone

The top panel shows prednisone binding to the GC receptor and performing transactivation and transrepression activities, depending on whether the complex binds, as a dimer, to DNA or, as a monomer, to a transcription factor. The bottom panel shows fosdagrocorat binding to the GC receptor. In this example the confirmation of the complex allows it to bind to transcription factors, enabling transrepression, but the complex is unable to bind to DNA, resulting in impaired transactivation activities compared with prednisone.

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GC, glucocorticoid; GRE, glucocorticoid-responsive elements.

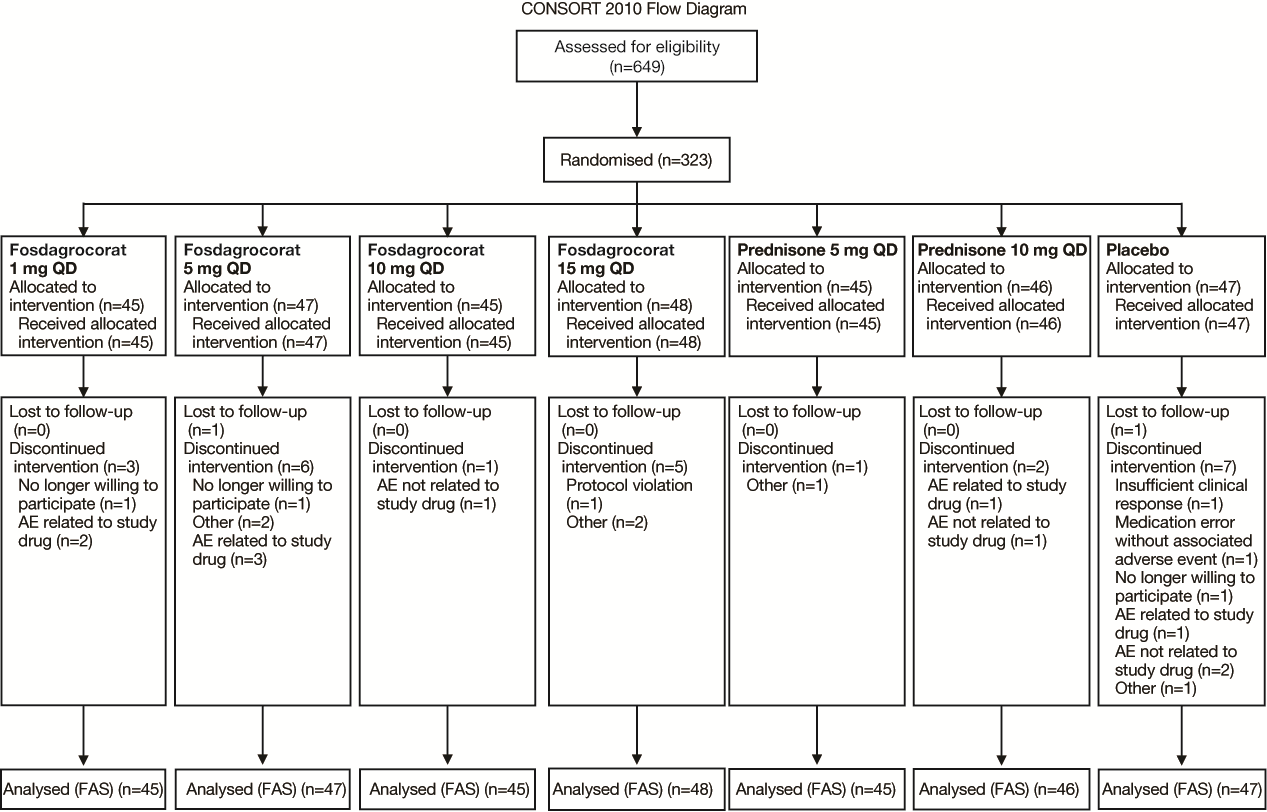
**Online supplementary figure S2** Study design

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Fosdagrocorat 1 and 5 mg tablets were the same size, fosdagrocorat 10 mg tablets were larger. Fosdagrocorat 15 mg doses were 1 × 5 mg and 1 × 10 mg tablets. Prednisone 5 mg was a capsule, the 10 mg dose was 2 × 5 mg capsules. To maintain blinding, patients received matching placebo for their non-randomised medications, with all patients taking two tablets and two capsules every day. For example, a patient randomised to fosdagrocorat 1 mg QD received 1 × fosdagrocorat 1 mg tablet, 1 × placebo for fosdagrocorat 10 mg tablet, and 2 × placebo for prednisone 5 mg tablets.

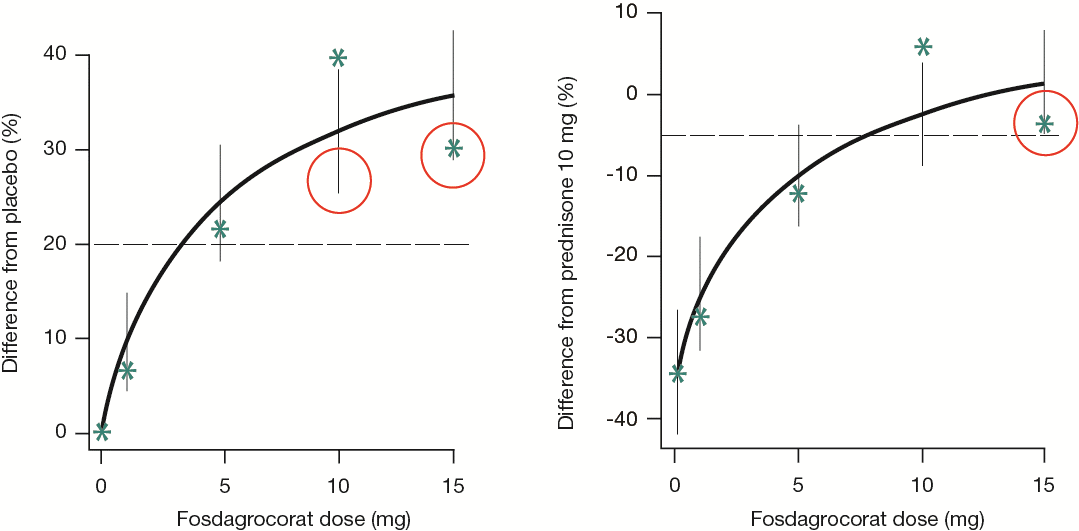
ACTH, adrenocorticotropic hormone; QD, once daily.

**Online supplementary figure S3** CONSORT diagram



AE, adverse event; FAS, full analysis set; QD, once daily.

**Online supplementary figure S4** Bayesian Emax dose–response model for ACR20 response rates at week 8 (FAS, NRI).



Asterisks represent ACR20 sample proportions and the corresponding points on the curve are the Emax model-based estimates. Bars are 60% credible intervals. Dotted lines represent the cut off in efficacy criteria (20% for placebo-corrected difference and –5% for prednisone 10‑mg-corrected difference). Red circles indicate doses meeting the cut-off criteria. NRI was used to handle missing data at Week 8. ACR20, American College of Rheumatology response criteria; Emax, maximum possible effect; FAS, full analysis set; NRI, non-responder imputation.

**Online supplementary figure S5**ACR component scores for a) tender joint count, b) swollen joint count, c) CRP levels, d) patient’s global assessment of arthritis, e) physician’s global assessment of arthritis and f) pain VAS

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All study treatments were administered once daily.

ACR, American College of Rheumatology; CRP, C-reactive protein; SD, standard deviation; VAS, visual analogue scale.

**Online supplementary figure S6** DAS28-4(CRP) and DAS28-3(CRP) mean and mean change from baseline over time (FAS): a) DAS28-4(CRP) mean over time, b) DAS28-4(CRP) mean change from baseline over time, c) DAS28-3(CRP) mean over time, and d) DAS28-3(CRP) mean change from baseline over time.

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All study treatments were administered once daily.

DAS28-3(CRP) and DAS28-4(CRP) both comprise: tender joint counts, swollen joint counts, and CRP. DAS28‑4(CRP) additionally includes patient global assessment of arthritis.

LS mean treatment difference (95% CI) from prednisone 10 mg change from baseline at Week 8 for fosdagrocorat 1, 5, 10, and 15 mg, respectively: 0.89 (0.37, 1.41), 0.37 (–0.15, 0.89), –0.09 (–0.61, 0.42), 0.05 (–0.46, 0.57). Estimates are derived from a mixed model with fixed effects for treatment, visit, treatment-by-visit interaction and baseline value.  
CI, confidence interval; DAS28-(CRP), disease activity score in 28 joints (C-reactive protein); FAS, full analysis set; LS, least squares; SD, standard deviation.

**Online supplementary figure S7** Bayesian Emax dose–response model for DAS28-4(CRP) at Week 8 (FAS, NRI)

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Asterisks represent sample means at Week 8 and corresponding points on the curve are model-based estimates. Bars are 80% credible intervals. LOCF was used to handle missing data at Week 8, if there was Week 4 and Week 6 data available. If Week 2 was the last available measurement, LOCF was not used and the Week 8 measurement remained missing.

DAS28-4(CRP), disease activity score in 28 joints (C-reactive protein); Emax, maximum possible effect; FAS, full analysis set; LOCF, last observation carried forward.

**Online supplementary figure S8** a) Mean and b) mean change from baseline in glucose metabolism biomarker fasting plasma glucose

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All study treatments were administered once daily.

SD, standard deviation.

**Online supplementary figureS9** Mean and mean change from baseline in blood cell counts: a)/b) Lymphocyte count, c)/d) neutrophil count, e)/f) eosinophil count

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All study treatments were administered once daily.

SD, standard deviation.

**Online supplementary figure S10**Plasma concentrations of the active metabolite of fosdagrocorat, PF-00251802, and its N-oxide metabolite PF-04015475. a) 0-hour post-dose plasma concentration of PF-00251802 over time, b) post-dose plasma concentration of PF-00251802 at Week 8, c) 0-hour post-dose plasma concentration of PF-04015475 over time, and d) post-dose plasma concentration of PF-04015475 at Week 8

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All study treatments were administered once daily.

SD, standard deviation.