GLORIA online supplementary appendix

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Supplementary tables

Online supplementary appendix Table s 1.
Additional baseline characteristics.

	prednisolone (n=224)	placebo (n=225)
general		
highest education level, n (%)		
primary school	62 (28)	73 (32)
secondary school	110 (49)	115 (51)
higher education	49 (22)	35 (16)
RA		
RF / anti-CCP, n (%)		
both –	57 (25)	45 (20)
RF +	148 (66)	151 (67)
anti-CCP +	119 (53)	134 (60)
both +	106 (47)	115 (51)
history, n (%)		
RA surgery	44 (20)	31 (14)
joint replacement	39 (17)	20 (9)
antirheumatic therapy		
previous		
DMARD	65 (29)	68 (30)
biologic	18 (8)	29 (13)
comorbidity		
all (including history), mean (SD)	3.3 (3.9)	3.1 (3.3)
median (q1-q3; max)	6 (4-9; 21)	5 (3-8; 26)
active, mean (SD)	2.2 (2.8)	2.0 (2.9)
median (q1-q3; max)	4 (2-6; 14)	3 (2-5; 15)
hypertension	123 (55)	113 (50)
diabetes	15 (7)	12 (5)
other cardiovascular	53 (24)	69 (31)
cataract	15 (7)	16 (7)
glaucoma	6 (3)	9 (4)
concomitant medication		
osteoporosis (excl. Ca/D)	28 (13)	30 (13)
anticoagulation	40 (18)	61 (27)
gastroprotection	118 (53)	110 (49)
hypertension	117 (52)	114 (51)
hypercholesterolemia	64 (29)	60 (27)
diabetes	14 (6)	18 (8)
total number of drugs/pt, mean median (range) (all indications)	7.0 7 (0-17)	7.1 7 (1-19)

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Online supplementary appendix Table s 2. Long-term effects in secondary outcome measures of disease activity (modified ITT population).

A. Primary model; B. Model with time-treatment interactions; C. Observed values.

The models are applied to create bootstrapped predictions of means at assessment, based on actual distribution of stratification factors, but excluding the random effect of center: this factor was not significant, but caused non-convergence in some iterations.
Results given as mean (SD); for the model-based predictions, baseline is set as the overall mean.
SDs are very similar for a specific measure over time, so a mean of these SDs is given at month 0.

Ranges: joint counts, 0-28; global assessments, pain fatigue: 0-10; HAQ 0-3. Abbreviations, see Table 3 in main manuscript.

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A. primary model	month cumulative prednisolone dose (mg)	0	3 455	6 910	12 1825	18 2735	24 3650
DAS28	prednisolone	4.52 (1.04)	3.26	3.06	2.89	3.03	2.97
	placebo	4.52 (1.04)	3.62	3.43	3.25	3.39	3.33
Components							
ESR	prednisolone	29 (15)	22	22	22	22	23
	placebo	29 (15)	26	26	26	27	27
Tender joint count	prednisolone	5.5 (3.7)	2.6	2.2	1.9	2.1	1.9
	placebo	5.5 (3.7)	2.9	2.5	2.2	2.4	2.2
Swollen joint count	prednisolone	3.3 (2.9)	1.3	1.0	0.8	0.8	0.5
	placebo	3.3 (2.9)	1.6	1.3	1.1	1.1	0.8
Patient global ass.	prednisolone	5.6 (2.3)	4.1	3.8	3.8	3.9	4.0
	placebo	5.6 (2.3)	4.5	4.2	4.2	4.3	4.4
Core set*							
Pain	prednisolone	5.4 (2.3)	4.0	3.8	3.7	3.8	3.8
	placebo	5.4 (2.3)	4.3	4.0	4.0	4.1	4.1
Fatigue	prednisolone	5.4 (2.2)	4.4	4.3	4.2	4.2	4.0
	placebo	5.4 (2.2)	4.4	4.3	4.2	4.2	4.0
Physician global ass.	prednisolone	4.7 (1.7)	2.7	2.3	2.1	2.2	2.1
	placebo	4.7 (1.7)	3.0	2.5	2.4	2.4	2.3
HAQ	prednisolone	1.2 (0.5)	1.0	1.1	1.0	1.0	1.1
	placebo	1.2 (0.5)	1.1	1.1	1.1	1.1	1.1
CRP	prednisolone	11.7 (10.8)	7.7	6.5	6.9	6.4	7.9
	placebo	11.7 (10.8)	8.7	7.5	7.9	7.4	8.9
SDAI	prednisolone	20.1 (7.1)	11.6	10.0	9.4	9.7	9.4
	placebo	20.1 (7.1)	12.7	11.1	10.5	10.8	10.5

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B. Model with time-treatment interactions	month	0	3	6	12	18	24
DAS28	prednisolone	4.52 (1.18)	3,17	3,05	2,90	3,15	3,08
	placebo	4.52 (1.18)	3,73	3,46	3,26	3,28	3,23
Components							
ESR	prednisolone	29 (17)	22	22	21	23	23
	placebo	29 (17)	26	26	27	26	27
Tender joint count	prednisolone	5.5 (4.1)	2.5	2.1	2.2	2.2	2.1
	placebo	5.5 (4.1)	3.1	2.8	2.0	2.3	2.1
Swollen joint count	prednisolone	3.3 (2.2)	1.1	1.0	0.8	1.0	0.7
	placebo	3.3 (2.2)	1.8	1.3	1.0	0.9	0.6
Patient global ass.	prednisolone	5.6 (2.6)	3.9	3.8	3.9	4.1	4.1
	placebo	5.6 (2.6)	4.7	4.2	4.1	4.2	4.3
Core set*							
Pain	prednisolone	5.4 (2.6)	3.8	3.9	3.7	3.9	4.0
	placebo	5.4 (2.6)	4.5	3.9	4.0	4.0	3.9
Fatigue	prednisolone	5.4 (2.5)	4.3	4.4	4.3	4.1	4.1
	placebo	5.4 (2.5)	4.6	4.2	4.1	4.3	4.0
Physician global ass.	prednisolone	4.7 (2.0)	2.6	2.3	2.1	2.3	2.2
	placebo	4.7 (2.0)	3.1	2.5	2.4	2.3	2.2
HAQ	prednisolone	1.2 (0.5)	1.0	1.1	1.0	1.1	1.1
	placebo	1.2 (0.5)	1.1	1.1	1.1	1.1	1.1
CRP	prednisolone	11.7 (13.2)	6.6	6.2	6.3	7.1	8.8
	placebo	11.7 (13.2)	9.5	7.6	8.3	6.5	7.7
SDAI	prednisolone	20.1 (8.4)	10.9	9.9	9.8	10.4	10.2
	placebo	20.1 (8.4)	13.6	11.4	10.2	10.3	9.8

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C. Observed values	month	0	3	6	12	18	24
	prednisolone | placebo observed n for DAS28	220| 221	205 | 201	190 | 182	162 | 165	137 | 143	134 | 121
DAS28	prednisolone	4.41 (1.03)	3.11 (1.27)	2.99 (1.21)	2.86 (1.13)	3.07 (1.27)	3.01 (1.16)
	placebo	4.60 (1.05)	3.78 (1.09)	3.54 (1.20)	3.28 (1.21)	3.29 (1.20)	3.24 (1.06)
Components							
ESR	prednisolone	28.9 (22.3)	–7.1 (19.1)	–6.3 (17.5)	–7.9 (17.9)	–6.1 (21.1)	–5.6 (18.6)†
	placebo	29.7 (20.6)	–3.1 (14.1)	–2.4 (15.6)	–2.2 (16.5)	–3.3 (18.0)	–1.4 (18.3)‡
Tender joint count	prednisolone	5.0 (4.4)	–2.6 (3.7)	–3.0 (4.4)	–3.0 (4.0)	–3.0 (4.6)	–3.1 (4.4)†
	placebo	5.9 (5.4)	–2.6 (5.6)	–3.0 (5.6)	–3.9 (5.6)	–3.5 (5.9)	–3.5 (5.1)‡
Swollen joint count	prednisolone	3.0 (3.2)	–1.9 (3.2)	–2.0 (2.7)	–2.3 (3.1)	–2.3 (3.6)	–2.5 (3.4)†
	placebo	3.6 (4.0)	–1.8 (3.6)	–2.4 (3.9)	–2.7 (4.1)	–2.9 (4.2)	–3.1 (3.6)
Patient global ass.	prednisolone	5.7 (2.4)	–1.8 (2.7)	–1.9 (2.8)	–1.8 (2.9)	–1.5 (2.8)	–1.4 (3.0)
	placebo	5.5 (2.2)	–0.8 (2.4)	–1.3 (3.0)	–1.3 (2.9)	–1.3 (2.8)	–1.1 (2.8)‡
Core set*							
Pain	prednisolone	5.5 (2.4)	–1.6 (2.6)	–1.5 (2.6)	–1.7 (2.8)	–1.4 (3.0)	–1.4 (2.8)†
	placebo	5.4 (2.3)	–0.9 (2.5)	–1.5 (2.9)	–1.4 (2.8)	–1.4 (2.8)	–1.4 (2.8)‡
Fatigue	prednisolone	5.2 (2.6)	–0.8 (2.4)	–0.8 (2.8)	–0.8 (2.8)	–1.0 (2.6)	–1.1 (2.8)†
	placebo	5.0 (2.8)	–0.5 (2.1)	–0.9 (2.4)	–0.9 (2.5)	–0.7 (2.7)	–1.0 (2.4)‡
Physician global ass.	prednisolone	4.6 (2.0)	–2.0 (2.2)	–2.3 (2.2)	–2.5 (2.3)	–2.4 (2.4)	–2.2 (2.2)
	placebo	4.7 (2.1)	–1.5 (2.1)	–2.1 (2.4)	–2.3 (2.4)	–2.4 (2.6)	–2.5 (2.4)‡
HAQ	prednisolone	1.3 (0.7)	–0.2 (0.4)	–0.2 (0.5)	–0.2 (0.6)	–0.2 (0.5)	–0.2 (0.6)†
	placebo	1.1 (0.7)	0.0 (0.4)	–0.1 (0.5)	–0.1 (0.5)	–0.1 (0.6)	–0.1 (0.6)‡
CRP	prednisolone	10.1 (16.0)	–3.4 (17.5)	–3.6 (16.1)	–3.1 (11.7)	–3.0 (19.9)	–1.1 (20.9)
	placebo	13.3 (20.0)	–3.6 (16.9)	–4.9 (18.7)	–4.3 (18.1)	–6.5 (18.5)	–5.3 (20.3)‡
SDAI	prednisolone	19.2 (8.7)	–8.7 (8.4)	–9.7 (8.3)	–9.8 (8.1)	–9.3 (10.1)	–9.1 (8.8)
	placebo	21.0 (11.1)	–7.0 (10.1)	–9.2 (10.6)	–10.7 (11.6)	–10.3 (12.3)	–10.8 (11.3)

† The sample size at 24 months in the prednisolone group was different from that of DAS28 for ESR (n=148), tender joints (n=150), swollen joints (n=150), pain (n=149), fatigue (n=149) and HAQ (n=152).

‡ The sample size at 24 months in the placebo group was different from that of DAS28 for ESR (n=133), tender joints (n=135), swollen joints (n=135), patient global (n=136), pain (n=147), fatigue (148), physician global (n=134), HAQ (n=147) and CRP (n=138).

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Online supplementary appendix Table s 3.
Open-label glucocorticoid (GC) treatment during trial.*

	all indications		for RA	
	prednisolone	placebo	prednisolone	placebo
per site				
oral	74	79	30	42
joints, bursae, tendons	43	46	26	27
intramuscular, subcutaneous	39	62	34	57
intravenous	4	2	0	0
total	160	189	90	126
patients	81	86	57	65
with substantial GC protocol deviations	7	12	4	9
mean events/pt			1.6	1.9
mean first administration (months after baseline)			13.0	8.5

* prednisolone, n=221; placebo, n=223.

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Online supplementary appendix Table s 4.
Other adverse events (AE) by organ class, and total of any AE, per 100 patient-years.

	prednisolone (n=224)	placebo (n=225)
Cardiac disorders	4.2	4.2
Eye disorders	6.2	5.6
Gastrointestinal disorders	20.8	14.6
General disorders and administration site conditions	12.6	10.9
Infections and infestations	28.9	21.9
Injury, poisoning and procedural complications	10.1	5.9
Investigations*	12.4	8.4
Metabolism and nutrition disorders	7.9	2.8
Musculoskeletal and connective tissue disorders	24.4	23.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2.5	2.2
Nervous system disorders	16.8	9.5
Respiratory, thoracic and mediastinal disorders	10.7	10.4
Skin and subcutaneous tissue disorders	17.4	8.4
Vascular disorders	7.9	4.2
Other	17.1	16.0
Total	200	148
Any AE (SAE, other AESI, and other AE)	278	205

SAE: serious adverse event. AESI: adverse event of special interest. Definition, see Methods.
* any abnormality on physical, lab or other examination.

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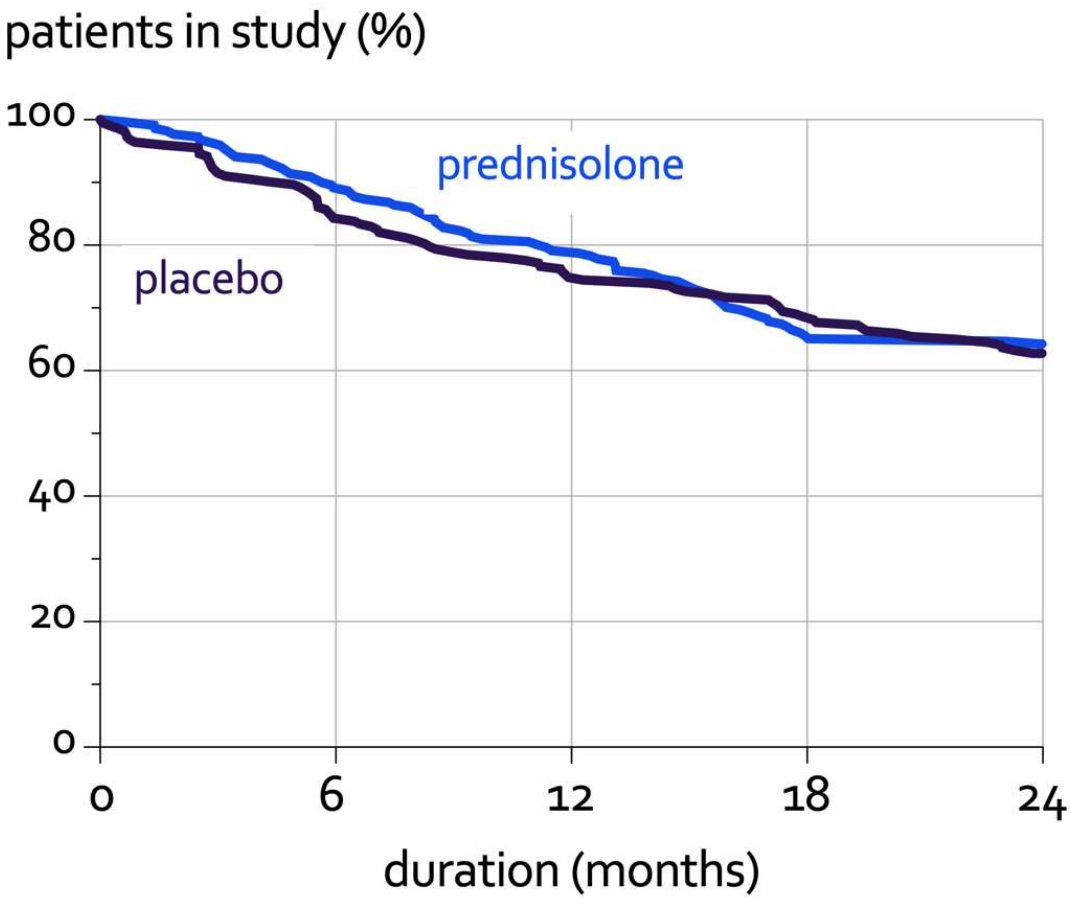
Supplementary figure

Online supplementary appendix Figure s 1.
Patients remaining in study.



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Detailed eligibility criteria (protocol 6.2, p.17)

Population (base)

RA patients of 65 years of age and older requiring antirheumatic therapy.

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- RA according to the 1987 or 2010 classification criteria of the American College of Rheumatology (ACR)
- and the European League Against Rheumatism (EULAR) (Aletaha D 2010);
- inadequate disease control, as evidenced by a 28-joint disease activity score (DAS28) of ≥ 2.60.* For eligibility, the DAS28 can be calculated with ESR or CRP, and also recalculated from the DAS of 44 joints. A DAS28 may be calculated with clinical and lab assessments obtained no more than 4 weeks before the baseline visit.
- age ≥ 65 years.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation:

Lower probability of benefit:

- Change, stop or start of antirheumatic treatment in the last month† prior to eligibility assessment, including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, intramuscular and oral gold, cyclosporine, biologic agents including anti-TNF, anakinra, abatacept, rituximab, tocilizumab (temporary exclusion);
- Treatment with systemic GC: oral or parenteral GC with a cumulative prednisolone equivalent dose of 200 mg or higher in the last 3 months (temporary exclusion);
- Treatment with any GC (oral, intra-articular, intravenous or intramuscular) in the last 30 days (temporary exclusion);
- Note: as this is a pragmatic trial, patients who require start of (other) antirheumatic treatment at baseline or during the trial can still be eligible (see protocol 7.2).

Higher probability of harm:

- Exposure to investigational therapy in the last three months;
- Current participation in another clinical trial;
- Major surgery, donation or loss of approximately 500 ml blood within 4 weeks prior to the screening visit (temporary exclusion);
- Absolute contraindication to low-dose prednisolone, as determined by the treating physician, such as: uncontrolled chronic infections, diabetes mellitus, hypertension, osteoporosis. When these conditions are under control (e.g. with antiosteoporosis drugs, antihypertensive drugs) these patients can enter;
- Absolute contraindication to Calcium and/or Vitamin D supplement as determined by the treating physician, such as: hyperparathyroidism (when insufficiently treated);
- Uncontrolled comorbid conditions, short life span, etc. as determined by the treating physician.

Difficulty to measure harm/benefit:

- Absolute indication to start with oral or intravenous GC, according to the treating physician;
- Inability to comply with medical instructions or inability to assess major outcomes at 6-monthly visits, in the assessment of the treating physician.

Subjects/patients not capable or willing to provide informed consent.

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* amended from original protocol: DAS28 ≥ 3.20

† amended from original protocol: last 3 months.

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Detailed randomization and masking procedure

We randomized patients (1:1) to receive prednisolone 5 mg/day or placebo for two years. A computer algorithm built into the electronic case record form software generated the randomization code based on minimization,17 and stratified for prior use of GC, start or change of antirheumatic medication at baseline, and center. More specifically, the algorithm assessed the range of allocated subjects for each stratification factor, and allocated the subject randomly if the sum of ranges was 3 or less; in case of a higher sum it allocated the subject so that the overall imbalance decreased. The center research nurse checked eligibility, completed the informed consent procedure and entered the stratification factors in the online electronic record form; the form then generated a unique patient ID, as well as a unique kit number. Our pharmaceutical partner allocated drug (verum or placebo) to kits with corresponding unique numbers. The pharmacy at each center received a sufficient supply of kits, each containing 90 capsules of study medication. Study medication constituted specially prepared opaque capsules that contained a prednisolone or placebo tablet. Through this procedure, study participants, care providers, and outcome assessors were blinded to treatment allocation. Success of blinding was not assessed. At data management one unblinded staff member was available to provide emergency unblinding when required.

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Detailed interpretation rules (statistical analysis plan 4.12, p. 25) and trial result

The outcomes of benefit (disease activity and damage progression)
and harm (number of patients with at least one SAE or other AESI) will be interpreted simultaneously.
The outcomes of benefit will be interpreted as follows (prednisolone group compared to placebo):

1. Success if either of the following conditions is met:
    1. lower disease activity AND lower damage score
    2. lower disease activity OR lower damage score; AND confounding

2. Partial success/tradeoff if either of the following conditions is met:
    1. lower disease activity OR lower damage score AND NO confounding
    2. NO lower disease AND NO lower damage progression AND confounding

3. Failure: NO lower disease activity AND NO lower damage score AND NO confounding.

The outcomes of harm will be interpreted as follows:

1. Success: NO significant increase in AEs

2. Failure: significant increase in AEs

Combined assessment of benefit and harm

1. Success: success in benefit and harm

2. Failure: failure in benefit and harm

3. Partial success/tradeoff: all other scenarios

Interpretation of trial results:

Both benefit endpoints were met (benefit condition 1.1) so there was a **success** for benefit.
The harm endpoint was met (harm condition 2) so there was a **failure** for harm.
The combined assessment result is therefore **partial success/tradeoff**.

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Modifications to trial protocol

(see also statistical analysis plan, 11. Appendix B)

1. Amendment 4 (feb 2019)
    a. Sample size adjustment (6.4)
    b. Specification of handling of co-interventions (7.2)
    c. Specification of follow up after trial (9.6)
    d. Specification of elective surgery as non-SAE (10.2.3)
2. Amendment 3 (may 2017)
    a. Eligibility increased:
        i. inclusion DAS28 lowered to '≥2.60' (6.2)
        ii. exclusion period for comedication shortened (6.3)
    b. Specification of handling of co-interventions (7.2)
    c. Specification of unblinding procedure (9.8)
3. Amendments 1&2: nonsubstantial (addition and closure of study sites)

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