

## Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA)

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# Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial



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## Summary

**Background** Individuals with serum antibodies to citrullinated protein antigens (ACPA), rheumatoid factor, and symptoms, such as inflammatory joint pain, are at high risk of developing rheumatoid arthritis. In the arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept (APIPPRA) trial, we aimed to evaluate the feasibility, efficacy, and acceptability of treating high risk individuals with the T-cell co-stimulation modulator abatacept.

**Methods** The APIPPRA study was a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial done in 28 hospital-based early arthritis clinics in the UK and three in the Netherlands. Participants (aged  $\geq 18$  years) at risk of rheumatoid arthritis positive for ACPA and rheumatoid factor with inflammatory joint pain were recruited. Exclusion criteria included previous episodes of clinical synovitis and previous use of corticosteroids or disease-modifying antirheumatic drugs. Participants were randomly assigned (1:1) using a computer-generated permuted block randomisation (block sizes of 2 and 4) stratified by sex, smoking, and country, to 125 mg abatacept subcutaneous injections weekly or placebo for 12 months, and then followed up for 12 months. Masking was achieved by providing four kits (identical in appearance and packaging) with pre-filled syringes with coded labels of abatacept or placebo every 3 months. The primary endpoint was the time to development of clinical synovitis in three or more joints or rheumatoid arthritis according to American College of Rheumatology and European Alliance of Associations for Rheumatology 2010 criteria, whichever was met first. Synovitis was confirmed by ultrasonography. Follow-up was completed on Jan 13, 2021. All participants meeting the intention-to-treat principle were included in the analysis. This trial was registered with EudraCT (2013–003413–18).

**Findings** Between Dec 22, 2014, and Jan 14, 2019, 280 individuals were evaluated for eligibility and, of 213 participants, 110 were randomly assigned to abatacept and 103 to placebo. During the treatment period, seven (6%) of 110 participants in the abatacept group and 30 (29%) of 103 participants in the placebo group met the primary endpoint. At 24 months, 27 (25%) of 110 participants in the abatacept group had progressed to rheumatoid arthritis, compared with 38 (37%) of 103 in the placebo group. The estimated proportion of participants remaining arthritis-free at 12 months was 92.8% (SE 2.6) in the abatacept group and 69.2% (4.7) in the placebo group. Kaplan–Meier arthritis-free survival plots over 24 months favoured abatacept (log-rank test  $p=0.044$ ). The difference in restricted mean survival time between groups was 53 days (95% CI 28–78;  $p<0.0001$ ) at 12 months and 99 days (95% CI 38–161;  $p=0.0016$ ) at 24 months in favour of abatacept. During treatment, abatacept was associated with improvements in pain scores, functional wellbeing, and quality-of-life measurements, as well as low scores of subclinical synovitis by ultrasonography, compared with placebo. However, the effects were not sustained at 24 months. Seven serious adverse events occurred in the abatacept group and 11 in the placebo group, including one death in each group deemed unrelated to treatment.

**Interpretation** Therapeutic intervention during the at-risk phase of rheumatoid arthritis is feasible, with acceptable safety profiles. T-cell co-stimulation modulation with abatacept for 12 months reduces progression to rheumatoid arthritis, with evidence of sustained efficacy beyond the treatment period, and with no new safety signals.

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## Introduction

Over the past decade, there has been progress in understanding the genetic, environmental, and immunological risk factors associated with rheumatoid arthritis,

and that individuals at high risk of disease can be identified by detecting serum autoantibodies to citrullinated protein antigens (ACPA) and symptoms, such as inflammatory joint pain.<sup>1,2</sup> Although the presence

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### Research in context

#### Evidence before this study

Although genetic and environmental risk factors associated with rheumatoid arthritis have been documented over many decades, clinical phenotypes of individuals at high risk have emerged from inception cohorts reported in the early 2000s. These studies described the risk of progression to rheumatoid arthritis associated with inflammatory joint pain, or arthralgia, in association with disease-associated serum autoantibodies. Since then, at-risk phenotypes have been reported by many groups with consistent rates of progression over 2 years in excess of 40%, or higher depending on whether additional modalities, such as imaging, were included as part of risk stratification. We searched PubMed, Embase, Cochrane Library, and clinical trial registries with the search terms “rheumatoid arthritis”, “prevention”, “arthralgia”, “anti-CCP”, and “randomized controlled trial” for studies published in English up until Jan 1, 2023.

#### Added value of this study

To our knowledge, the APIPPRA study is the first randomised controlled trial to test the effects of co-stimulation modulation on the progression of a high-risk state to rheumatoid arthritis.

By contrast with previous trials, the APIPPRA study suggests that a subset of individuals at high risk exists who benefit from abatacept beyond the treatment period. In-depth analysis of patient-reported outcomes reveals that the symptom burden characteristic of ACPA-positive individuals with arthralgia is driven, at least in part, by systemic adaptive immune responses targeted by abatacept. These symptom complexes include not only pain, function, and wellbeing, but also sleep problems, anxiety, and work instability. Co-stimulation modulation also reverses subclinical inflammation defined by ultrasonography. The outcome of a 12-month fixed dosing period suggests that longer periods of treatment may be required to prevent progression to rheumatoid arthritis.

#### Implications of all the available evidence

Our results show that rheumatoid arthritis prevention trials are feasible and targeting adaptive immunity at an early stage, before clinically apparent arthritis is manifest, can prevent the onset of rheumatoid arthritis. The data provide a framework for future prevention trials and a realistic proposition for disease prevention in routine clinical care.

of autoantibodies might precede disease onset by a decade or more, the combination of ACPA with symptoms, and evidence of subclinical synovitis by imaging, has increased the predictive power of identifying individuals who are most likely to progress to rheumatoid arthritis within 2 years.<sup>3,4</sup> These features have provided a framework for evaluating therapeutic strategies that could delay or prevent disease onset.<sup>5</sup>

Abatacept is a biological disease-modifying antirheumatic drug recommended for the treatment of rheumatoid arthritis that selectively modulates co-stimulatory signals required for T-cell activation.<sup>6</sup> By binding to CD80 or CD86, abatacept down-modulates CD28-mediated co-stimulation of T cells, suppressing persistent T-cell activity involved in the pathogenesis of immune-mediated inflammatory diseases.<sup>7</sup> Abatacept has shown efficacy in the treatment of active rheumatoid arthritis when used as monotherapy or in combination with conventional disease-modifying antirheumatic drugs in patients with an inadequate response to other conventional or biological disease-modifying antirheumatic drugs.<sup>6,8</sup> Other studies suggest that abatacept has efficacy in patients with early rheumatoid arthritis (ie, symptom duration <18 months),<sup>9,10</sup> with increased frequency of responses in patients with high ACPA concentrations.<sup>11</sup> These data suggest that co-stimulatory signals play an important role in perpetuating the early phase of the disease. Given the mechanism of action of abatacept and the likely role of T cells in the earliest detectable phase of disease, we aimed to investigate abatacept in individuals at high risk of developing rheumatoid arthritis.

## Methods

### Study design

The APIPPRA study was a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial undertaken in 28 hospital-based early arthritis clinics in the UK and three in the Netherlands. The trial protocol was approved by the national regulatory authorities in the UK (National Research Ethics Service Committee London, Westminster; 14/LO/0100) and the Netherlands (Leiden University Medical Centre Medical Ethics Committee). The study was conducted according to the International Council for Harmonisation guidelines, applicable regulations and guidelines governing the conduct of clinical trials, and the principles of the Declaration of Helsinki. Trial oversight was provided by independent trial steering and data monitoring committees. The study protocol has been reported previously.<sup>12</sup>

### Participants

Adults aged 18 years or older, at risk of developing rheumatoid arthritis, were recruited on the basis of clinical and laboratory characteristics. Key inclusion criteria were the presence of inflammatory joint pain (see study protocol for definition) and testing positive for ACPA and rheumatoid factor, regardless of the assay used in local laboratories. Individuals who were negative for rheumatoid factor but had ACPA concentrations three or more times the upper limit of normal were also eligible. Individuals with a previous diagnosis of inflammatory arthritis, or previous use of disease-modifying antirheumatic drugs or corticosteroids, were excluded

from the study. Simple analgesics or non-steroidal anti-inflammatory drugs were permitted. Individuals with clinically apparent inflammatory arthritis, characterised by soft tissue swelling of one or more synovial joints before random assignment, were also excluded. Subclinical synovitis, detected by ultrasonography or MRI, was not an exclusion criterion. A complete list of eligibility criteria can be found in the published protocol.<sup>12</sup> Study participants provided written informed consent before screening assessments and randomisation.

### Randomisation and masking

The King's Clinical Trials Unit randomly assigned participants (1:1) using computer-generated permuted block randomisation (block sizes of 2 and 4) stratified by sex (male and female), smoking (never, former, and current), and country (UK and Netherlands). This unit also oversaw the trial and data management. Masking was achieved through the provision of four kits of abatacept or matching placebo to participants every 3 months. Each kit was identical in appearance and packaging containing four pre-filled syringes with coded labels. Participants, investigators, subinvestigators, clinical assessors, sonographers, and hospital trial pharmacists who distributed the study drug were masked to group assignment.

### Procedures

Participants were randomly assigned to abatacept 125 mg subcutaneous injections weekly as recommended for rheumatoid arthritis treatment,<sup>6,8</sup> or placebo for 12 months.<sup>12</sup> Participants were trained to self-administer the study drug subcutaneously using a single-dose pre-filled syringe according to local practices. Treatment compliance was evaluated at study visits every 3 months and by completing study medication diaries. After 12 months, the study drug was discontinued, and participants were followed up for a further 12 months. When rheumatoid arthritis was diagnosed, the study drug was withdrawn, and treatment was initiated at the discretion of the supervising investigator. Otherwise, disease-modifying antirheumatic drugs and corticosteroids were not permitted at any time during the study.

Following baseline clinical and imaging assessments, participants attended follow-up every 3 months for evaluation of symptoms and signs of inflammatory arthritis, completion of questionnaires, and patient-reported outcomes, regardless of whether they met the primary outcome. Blood was taken for disease activity assessments, routine toxicity monitoring, and biomarker studies. Radiographs of hands and feet were completed at baseline, 12 months, and 24 months, and sub-clinical synovitis was assessed via ultrasonography of 24 predefined joints every 6 months until the end of the study, or until the primary endpoint was met (appendix pp 4–6). Clinical assessors were masked to ultrasound

assessment and the ultrasonographers were masked to the clinical assessments.

### Outcomes

The primary endpoint was the time to development of clinical synovitis in three or more joints or rheumatoid arthritis according to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 criteria,<sup>13</sup> whichever was met first, and where joint involvement was defined as joint swelling determined by two independent assessors. In either case, synovitis in nominated joints was confirmed by ultrasonography. Time was censored at 24 months or earlier withdrawal. A primary endpoint roadmap is provided in the appendix (p 3).

Secondary endpoints included Disease Activity Scores (DAS 28). These scores incorporated tender and swollen joint counts, patient global Visual Analogue Score (VAS), C-reactive protein or erythrocyte sedimentation rate, and extended 68 or 66 joint counts, simple DAS and clinical DAS, pain VAS, lifestyle factors questionnaire, Health Assessment Questionnaire (HAQ), EQ-5D, Hospital Anxiety and Depression Scale (HADS), Rheumatoid Arthritis Work Instability Scale (RA-WIS), Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) questionnaire, the Illness Perception Questionnaire modified for Rheumatoid Arthritis (IPQ-R), and the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire. Additional secondary outcomes were the proportion of participants requiring disease-modifying antirheumatic drugs or corticosteroid therapy and the time to commencing therapy. Imaging assessments included x-rays of hands and feet at baseline, 12 months, and 24 months using van der Heijde Sharpe Modified Scores for erosions and joint space narrowing,<sup>14</sup> scored by readers in random-time order, and evaluation of synovial hypertrophy (grayscale) and vascularity (power Doppler) defined by ultrasonography incorporating EULAR-OMERACT combined severity grading (appendix pp 5–6).<sup>15</sup>

Clinical assessments of safety were recorded at all visits. The severity of adverse events and their relation to the study drug were reviewed regularly by an independent data monitoring committee.

### Statistical analysis

The power calculations were based on 40% of participants in the placebo group developing arthritis over 24 months, informed by at-risk cohorts.<sup>16</sup> 172 participants were needed to provide 80% power to detect a 50% relative reduction in developing arthritis in the abatacept group compared with the placebo group (hazard ratio [HR] 0·437), based on a two-sided log-rank test at the 5% significance level, without loss to follow-up of any of the required 52 events. By applying a conservative inflation of 20% to allow for dropout, we aimed to recruit 103 participants per group.

See Online for appendix

The primary analysis followed the intention-to-treat principle (ie, included all randomly assigned participants using available follow-up data). For the primary outcome, a per-protocol analysis was done of eligible participants who complied with at least 90% injections and did not use forbidden rescue medication. Sensitivity analyses were done for missing data<sup>17</sup> and potential informative dropout. Kaplan–Meier survival curves for 12-month or 24-month outcomes were censored at the corresponding 2-week per-protocol window, or at dropout if earlier than this. These survival curves were used to estimate the proportion in each group remaining arthritis-free, reported as percentage (SE). A stratified Cox proportional

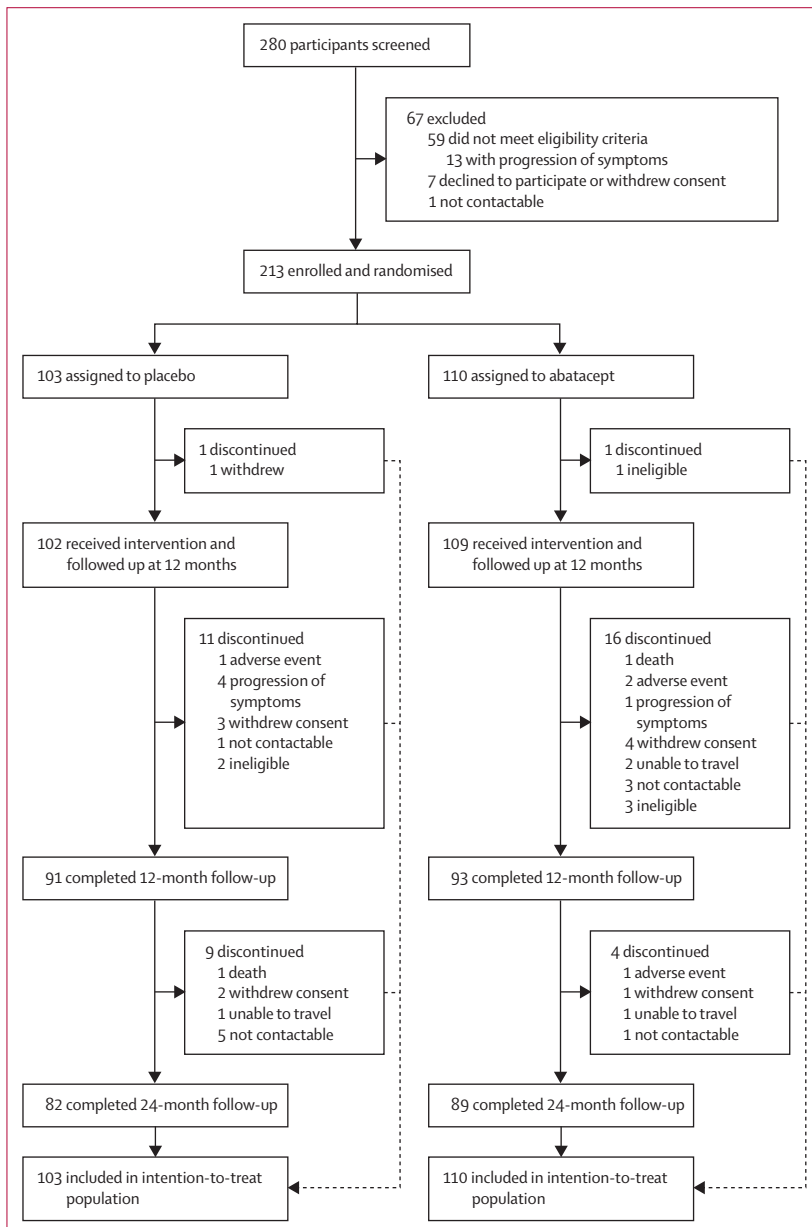


Figure 1: Trial profile

	Placebo (n=103)	Abatacept (n=110)
<b>Sex</b>		
Male	22 (21%)	26 (24%)
Female	81 (79%)	84 (76%)
<b>Age, years</b>		
	48·8 (10·9)	48·3 (11·6)
<b>BMI, kg/m<sup>2</sup></b>		
	28·9 (6·4)	27·0 (5·1)
<b>Country</b>		
UK	99 (96%)	102 (93%)
Netherlands	4 (4%)	8 (7%)
<b>Ethnicity</b>		
White	85 (82%)	89 (81%)
Mixed	2 (2%)	3 (3%)
Asian	9 (9%)	11 (10%)
Black	6 (6%)	7 (6%)
Other	1 (1%)	0
<b>Smoking status</b>		
Never	35 (34%)	45 (41%)
Previous	47 (46%)	44 (40%)
Current	21 (20%)	21 (19%)
<b>Alcohol consumption per week, units*</b>		
None	21/101 (21%)	24/104 (23%)
1–5	44/101 (44%)	48/104 (46%)
6–10	17/101 (17%)	17/104 (16%)
11–15	6/101 (6%)	8/104 (8%)
16–20	8/101 (8%)	6/104 (6%)
>20	5/101 (5%)	1/104 (1%)
<b>Serology</b>		
Positive for ACPA and RF	93 (90%)	90 (82%)
ACPA (≥3 ULN) and RF negative	9 (9%)	19 (17%)
ACPA (≥3 ULN) and RF positive or negative	96 (93%)	103 (94%)
ACPA (<3 ULN) and RF negative	1 (1%)†	0
ACPA negative and RF positive	0	1 (1%)†
<b>Swollen joint count*</b>		
66 joints	0 (0–0); 103	0 (0–0); 108
28 joints	0 (0–0); 103	0 (0–0); 108
<b>Tender joint count*</b>		
68 joints	2 (0–6); 103	1 (0–5); 108
28 joints	1 (0–3); 103	1 (0–3); 108
<b>PGA (0–100)*</b>		
	16 (4–48); 103	15 (2–44); 107
<b>EGA (0–100)*</b>		
	10 (2–29); 103	11 (2–23); 107
<b>Pain VAS (0–100)*</b>		
	15 (3–35); 103	20 (2–39); 107
<b>Erythrocyte sedimentation rate, mm/h*</b>		
	13·0 (6·5–21·0); 73	14·0 (8·0–26·5); 81
<b>C-reactive protein, mg/dL*</b>		
	4 (2–6); 72	4 (2–6); 81

Data are n (%), n/N (%), mean (SD), or median (IQR); n. ACPA=antibodies to citrullinated protein antigens. EGA = Evaluator Global Assessment. PGA=Patient Global Assessment. RF=rheumatoid factor. ULN=upper limit of normal. VAS=Visual Analogue Scale. \*Data were not available for all randomly assigned participants. †Randomly assigned participants but not eligible at entry.

**Table 1: Baseline characteristics of the intention-to-treat population**



hazards regression model, accounting for randomisation stratifiers, was planned but with few events in most randomisation strata, the unadjusted model alone was used. Proportional hazards assumptions were assessed graphically (log-log plot) and tested by log-of-time interaction; failure led to reporting restricted mean survival times. Linear mixed effects models were planned for continuous outcomes and differences in proportions for binary outcomes (appendix p 2). Since the distribution of swollen joint counts was markedly skewed, the Kaplan-Meier method was used to estimate the proportions of patients developing one, two, or three swollen joints.

All tests were two-tailed and primarily assessed at the 5% significance level. The trial was powered to allow a secondary 1% significance level to be applied to allow safer interpretation of multiple secondary outcomes. Descriptive statistics were reported for measures of acceptability, feasibility, and safety, and percentage measures reported with 95% CIs. There were no interim analyses or stopping rules. Analyses were performed in SPSS (version 28) and the statistical analysis plan was reviewed and signed off by the trial steering and data monitoring committees before data lock.

The trial was registered with EudraCT (2013-003413-18).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

Between Dec 22, 2014, and Jan 14, 2019, 280 individuals were enrolled, and of 213 participants, 110 were randomly assigned to abatacept and 103 to placebo (figure 1). Of 59 participants who did not meet eligibility criteria, 13 had progression of symptoms, including development of clinical arthritis. Seven participants declined to participate and one could not be contacted. Overall, 42 participants withdrew (21 in each group), 32 before and ten after a primary event. 89 (81%) of 110 participants in the abatacept group and 82 (80%) of 103 participants in the placebo group completed the study (appendix p 7). All 213 participants were included in the intention-to-treat analysis.

Mean age was 48.5 years (SD 11.2) and, of 213 participants, 165 (77%) were female and 48 (23%) were male (table 1). Randomisation stratifiers were evenly balanced between the groups. Adherence to study medication was similar between groups, with 81 (74%) of 110 participants in the abatacept group and 77 (75%) of 103 participants in the placebo group administering 90% or more injections in 12 months or until the primary endpoint was met. This translates to non-adherence rates of 26% and 25% for the abatacept and placebo groups, respectively.

In the intention-to-treat analysis of primary outcomes, seven (6%) of 110 participants in the abatacept group and

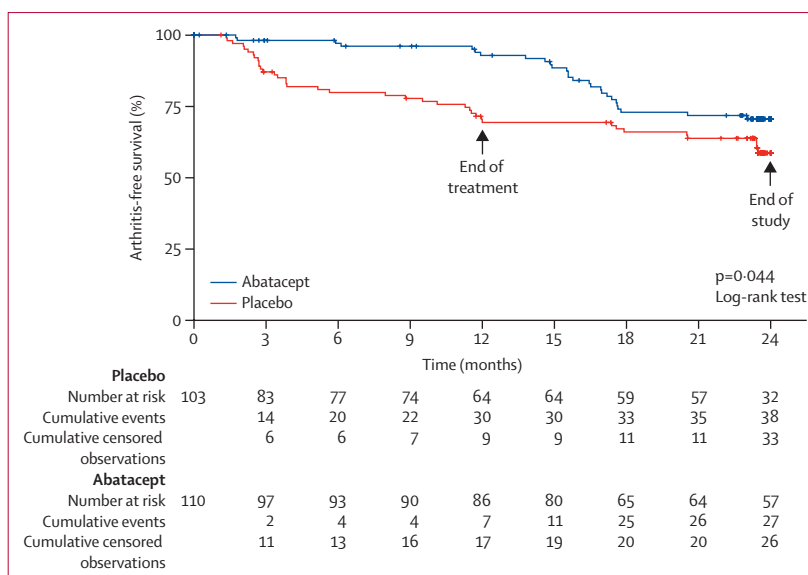


Figure 2: Arthritis-free survival by group

30 (29%) of 103 participants in the placebo group met the primary endpoint by 12 months. These proportions increased to 27 (25%) of 110 participants for abatacept and 38 (37%) of 103 participants for placebo at 24 months. Kaplan-Meier arthritis-free survival plots showed differences between groups at 24 months in favour of abatacept treatment (time-to-event log-rank test,  $p=0.044$ ; figure 2). The estimated proportion of participants remaining arthritis-free at 12 months was 92.8% (SE 2.6) in the abatacept group and 69.2% (4.7) in the placebo group. By 24 months, it was 70.4% (4.8) and 58.5% (5.4) for the abatacept and placebo groups, respectively.

Although the unadjusted Cox regression model for the study period provided an HR of 0.61 (95% CI 0.37–0.99) in favour of abatacept compared with placebo, the proportional hazards assumption for the study period was not met ( $p=0.0025$ ). For the first 12 months, the assumption held, with the model providing a HR of 0.20 (95% CI 0.09–0.45). Therefore, the restricted mean survival time was used as a pre-specified summary statistic (appendix p 2).<sup>18</sup> At 24 months, the restricted mean survival time was 658 days (SE 16) for abatacept and 558 days (27) for placebo, with a difference in restricted mean arthritis-free survival of 99 days (95% CI 38–161;  $p=0.0016$ ). For the 12-month treatment period, the restricted mean survival time was 368 days (SE 5) for abatacept and 316 days (12) for placebo, with a difference in restricted mean arthritis-free survival of 53 days (95% CI 28–78;  $p<0.0001$ ). Further analysis at 6 months and 18 months indicated that the effect persisted throughout the study (appendix p 8). The per-protocol analysis of treatment-compliant individuals showed similar results (difference in restricted mean survival

time between groups at 24 months was 114 days [95% CI 43–185;  $p=0.0018$ ]. Additional sensitivity analysis of the primary outcome criteria is described in the appendix (pp 8–9).

In total, 80 participants took disease-modifying antirheumatic drugs or corticosteroids during the study. Of those who met the primary endpoint, 26 (96%) of 27 participants in the abatacept group and 34 (90%) of 38 participants in the placebo group then took disease-modifying antirheumatic drugs or steroids. Ten additional participants in each group took disease-modifying antirheumatic drugs or steroids as forbidden medication (ie, medication that was not permitted according to the study protocol). The proportion of participants taking these drugs at 12 months was 12.2% (SE 3.3) in the abatacept group and 33.4% (4.8) in the placebo group (difference –21.2%, 95% CI –32.7 to –9.7). At 24 months,

38.2% (SE 5.0) and 47.6% (5.3) took the drugs in each group, respectively (difference –9.4%, 95% CI –23.7 to 4.9; appendix p 10). The restricted mean survival times taking first disease-modifying antirheumatic drug to taking corticosteroid were shown to be higher in the abatacept group at 12 months and 24 months (appendix p 10).

At 12 months, the proportions of participants in the placebo group with greater than or equal to one, two, or three swollen joints were appreciably higher than those in the abatacept group. At 24 months, the difference between groups was less substantial (table 2; appendix p 11). Reductions in pain VAS and DAS-28 were also greater with abatacept than placebo at the end of the treatment period, but were not sustained to 24 months. Changes in tender joint count, clinical disease activity score, and simple disease activity score did not differ significantly between groups.

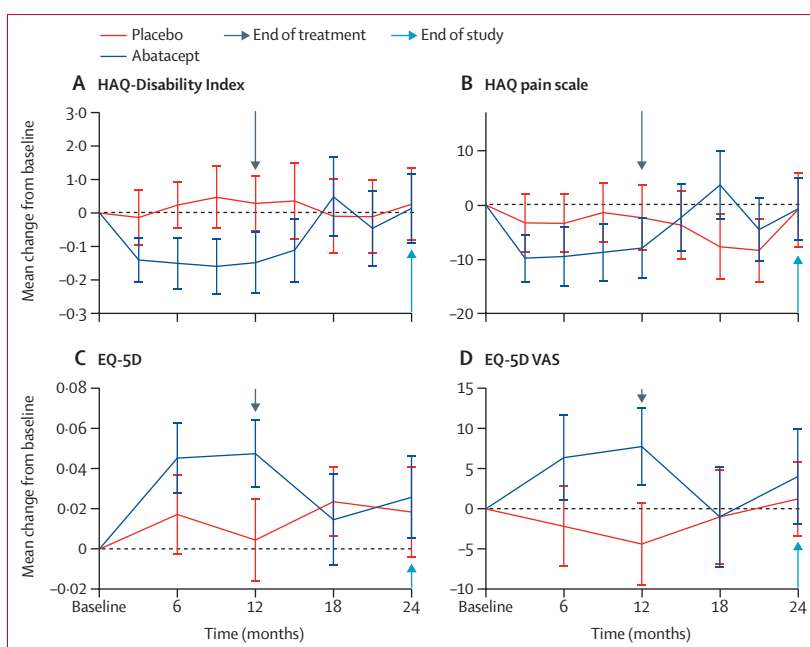
	Placebo (n=103)			Abatacept (n=110)			Difference (95% CI) *	
	Baseline	12 months	24 months	Baseline	12 months	24 months	12 months	24 months
Tender joint count (0–68)†	2 (0–6); 103	1 (0–4); 91	1 (0–6); 79	1 (0–5); 108	0 (0–2); 90	1 (0–5); 87	-1.63 (-3.98 to 0.71)	1.35 (-0.95 to 3.65)
Swollen joints‡								
≥1	0	46.0 (5.0)	62.0 (5.1)	0	18.9 (3.6)	50.5 (5.1)	-27.1 (-39.1 to -15.0)	-11.5 (-25.6 to 2.7)
≥2	0	32.9 (5.0)	47.9 (5.1)	0	10.4 (3.6)	33.3 (5.1)	-22.5 (-34.5 to -10.4)	-14.6 (-28.7 to -0.5)
≥3	0	27.7 (5.0)	38.4 (5.1)	0	3.1 (3.6)	25.3 (5.1)	-24.6 (-36.7 to -12.6)	-13.1 (-27.2 to 1.0)
Pain VAS	24.9 (25.1); 103	23.4 (2.7); 90	21.4 (3.0); 70	23.1 (21.4); 107	13.2 (2.1); 88	21.3 (2.8); 87	-8.1 (-14.3 to -1.9)	1.5 (-5.8 to 8.8)
HAQ-DI§	0.52 (0.68); 103	0.53 (0.07); 91	0.52 (0.08); 81	0.65 (0.71); 109	0.42 (0.06); 89	0.56 (0.07); 88	-0.14 (-0.26 to -0.03)	0.03 (-0.11 to 0.17)
HAQ pain§	31.0 (26.8); 101	27.3 (2.9); 91	27.7 (3.3); 79	29.4 (26.6); 107	18.0 (2.7); 88	25.2 (3.2); 86	-7.9 (-15.0 to -0.8)	-0.2 (-8.2 to 7.7)
EQ-5D¶	0.86 (0.10); 103	0.87 (0.01); 88	0.89 (0.01); 78	0.86 (0.10); 110	0.92 (0.01); 88	0.89 (0.01); 89	0.05 (0.02 to 0.07)	0.01 (-0.02 to 0.03)
EQ-5D VAS¶	72.0 (21.0); 100	68.4 (2.7); 90	74.0 (2.7); 81	69.1 (23.5); 108	79.4 (2.1); 89	75.7 (2.5); 89	12.32 (6.19 to 18.44)	2.79 (-3.99 to 9.57)
HADS-A	5.8 (4.2); 103	6.2 (0.5); 89	5.4 (0.5); 79	5.7 (3.7); 110	4.9 (0.4); 88	5.5 (0.4); 89	-1.26 (-2.15 to -0.37)	-0.13 (-1.11 to 0.86)
HADS-D	3.7 (3.2); 103	4.1 (0.5); 89	3.6 (0.4); 79	3.7 (3.3); 110	3.4 (0.4); 88	3.8 (0.4); 89	-0.67 (-1.43 to 0.10)	0.12 (-0.72 to 0.95)
FACIT-F**	118.9 (26.7); 99	118.4 (3.3); 88	121.6 (3.4); 79	114.2 (27.7); 108	124.3 (2.9); 89	120.6 (2.9); 89	9.53 (3.88 to 15.17)	2.04 (-4.19 to 8.27)
SPARRA††								
Joint pain	89% (65/73)	84% (53/63)	..	95% (72/76)	59% (45/76)	..	-24.9% (-39.2 to -10.7)	..
Joint stiffness	83% (60/72)	71% (45/63)	..	83% (64/77)	57% (43/75)	..	-14.1% (-29.9 to 1.7)	..
Joint swelling	51% (37/72)	55% (34/62)	..	53% (40/75)	32% (24/76)	..	-23.3% (-39.5 to -7.1)	..
Weakness and loss of strength	65% (46/71)	58% (36/62)	..	66% (51/77)	43% (32/74)	..	-14.8% (-31.5 to 1.9)	..
Fatigue	66% (47/71)	69% (42/61)	..	66% (51/77)	60% (45/75)	..	-8.9% (-24.9 to 7.2)	..
Sleep problems	61% (43/71)	74% (46/62)	..	56% (43/77)	53% (40/75)	..	-20.9% (-36.5 to -5.2)	..
RA-WIS	7.6 (6.6); 91	7.7 (0.8); 83	5.8 (0.8); 73	7.9 (6.9); 104	5.8 (0.7); 87	6.8 (0.7); 84	-1.70 (-3.21 to -0.18)	1.03 (-0.69 to 2.75)

Data are mean (SD) or % (n/N) for baseline and mean (SE) or % (n/N) for 12 months and 24 months, or median (IQR) for tender joint count. Participant numbers are also provided. Descriptive statistics are summarised in the appendix (pp 8–11). FACIT-F=Functional Assessment of Chronic Illness Therapy—Fatigue. HADS-A=Hospital Anxiety and Depression Scale—Anxiety. HADS-D=Hospital Anxiety and Depression Scale—Depression. HAQ-DI=Health Assessment Questionnaire Disability Index. RA-WIS=rheumatoid arthritis work instability scale. SPARRA=Symptoms in Persons At Risk of Rheumatoid Arthritis. VAS=Visual Analogue Scale. \*Models were adjusted for the baseline of the outcome, stratifiers (sex and smoking status), and the missing indicator method, except for the SPARRA questionnaire and swollen joints outcomes. †The distribution of the tender joint count was skewed, with 94 (52%) of 181 participants with no tender joints at 12 months and 74 (45%) of 166 at 24 months. Sensitivity analysis reanalysing the data in the square root scale confirmed these results. ‡The distribution of the swollen joint count at all follow-up timepoints was highly skewed with 147 (81%) of 181 participants having no swollen joints at 12 months and 125 (75%) of 166 at 24 months, with some outliers. §For HAQ, the model was tested on 202 participants for HAQ-DI (subscale 0–3) and on 201 for the HAQ pain scale (subscale 0–100). See the appendix (p 8) for the breakdown of outcomes at each study visit. ¶For EQ-5D, there were 193 participants tested in the model (for breakdown of outcomes at each study visit see the appendix [p 9]). ||For HADS (subscale 0–3 for each of seven items), the model was tested on 193 participants. \*\*For FACIT, models were fitted in 193 participants. The breakdown of outcomes by subdomain is shown in the appendix (p 10). ††In the SPARRA questionnaire, proportions of participants with duration of symptoms of at least 1 day in the past month are shown for those symptoms captured in ≥50% of participants. Evaluation of symptom complexes using the SPARRA questionnaire was defined only at baseline and 12 months.

Table 2: Effect of co-stimulation modulation on the symptom burden of individuals at risk of rheumatoid arthritis

There were consistent patterns of response in favour of abatacept at 12 months for function and pain (as determined by HAQ); emotional wellbeing and quality of life (EQ-5D); anxiety (but not the depression component of the HADS; table 2); FACIT-F total scores; physical, emotional, and functional wellbeing (appendix p 12); and two of the IPQ-R domains (appendix p 13). These effects were not sustained by 24 months. Typical changes over time for HAQ and EQ-5D are shown in figure 3 in which significant differences in favour of abatacept were observed at 12 months. These differences were not sustained by 24 months. Symptom complexes using the SPARRA questionnaire revealed that after 12 months of treatment, a smaller proportion of participants had symptoms for at least 1 day in the past month in the abatacept group, with improvements of 20% or more for joint pain, perception of joint swelling, and sleep problems (table 2). There was a reduction in work instability favouring abatacept at 12 months, but not at 24 months.

At baseline, van der Heijde modified Sharp radiographic scores of 0 were recorded in 176 (84%) of 209 participants for erosions and in 191 (91%) of 209 participants for joint space narrowing (appendix p 16). From the distribution of erosion scores, 197 (94%) of 209 participants had erosion scores of 1 or less (appendix p 17). A between-groups comparison of the proportion of participants whose scores worsened by at least 1 point at 12 months and 24 months found that the numbers were too small for a meaningful analysis (appendix pp 15–16). Sonographic analysis revealed that at baseline, 70 (33%) of 212 participants had no detectable synovial hypertrophy (grayscale) and 154 (73%) of 212 participants had no detectable vascularity (power Doppler; table 3). At the end of treatment, fewer participants in the abatacept group had grayscale or power Doppler scores that worsened by 1 point from baseline when compared with the placebo group. This effect was not sustained 12 months after stopping treatment. Due to the discontinuation of ultrasonography from when the primary event was met, a composite outcome was generated, defined as the occurrence of a primary event or worsening by 1 point from baseline of the grayscale score by ultrasonography. A significantly lower proportion of participants in the abatacept group than the placebo group met this composite outcome at 12 months and 24 months (table 3). Similar results were observed for power Doppler at 12 months but not 24 months. Using EULAR-OMERACT severity grading,<sup>15</sup> significantly fewer participants in the abatacept group had worsening of severity scores or a primary event, an effect that was sustained to 24 months. Scores for tenosynovitis of hands and wrists were low at baseline, with maximum grayscale scores of 2 or more being detected in only four (4%) of 91 participants in the placebo group and nine (9%) of 100 in the abatacept group; for power Doppler, three (3%) of 87 participants and six (6%) of 96 participants had scores of 2 or higher. These scores remained low at follow-up in both groups.



**Figure 3:** Mean change from baseline for secondary outcomes over 24 months

HAQ-Disability Index (A), HAQ pain scale (B), EQ-5D (C), and EQ-5D VAS (D), over 24 months. The end of study and end of treatment are indicated. SD at baseline for these measures are 0.7 for HAQ-Disability Index, 2.6.7 for HAQ pain scale, 0.10 for EQ-5D, and 2.2.3 for EQ-5D VAS. HAQ=Health Assessment Questionnaire. VAS=Visual Analogue Scale.

Taken together, serial sonographic assessments showed that abatacept reduces the progression of subclinical disease and the effects were partly sustained beyond the treatment period.

Of those participants receiving at least one dose of study drug, 100 (92%) of 109 participants in the abatacept group and 91 (89%) of 102 participants in the placebo group had at least one adverse event, and 57 (52%) of 109 and 62 (61%) of 102 had at least one infection (table 4; appendix p 18). The frequency was similar between groups, apart from gastrointestinal, haematological, neurological, and other adverse events, which were higher in the abatacept group. All six serious adverse events related to study drug were reported in the abatacept group, and included genitourinary infection (n=1), ear infection (n=1), nausea (n=1), dry mouth (n=1), fatigue (n=1), and headache (n=1). Laboratory adverse events were infrequent, and similar between groups.

18 serious adverse events were reported (table 4). In the abatacept group, these were death (n=1), cardiovascular events (n=1), admission for joint replacement surgery (n=2), and malignancy (n=3), and in the placebo group, these were death (n=1), infections (n=3), cardiovascular events (n=2), venous thromboembolism (n=1), malignancy (n=1), and admission for joint replacement surgery (n=3). All serious adverse events were deemed unrelated or unlikely to be related to study medication. There were six pregnancies in the abatacept group and one in the placebo group. Of the participants receiving at least one dose of study drug, four withdrew due to adverse events (three



	Baseline (n=212)		12 months (n=155)		Difference (95% CI)	24 months (n=107)		Difference (95% CI)
	Placebo	Abatacept	Placebo	Abatacept		Placebo	Abatacept	
Grayscale maximum score								
0	31% (32/103)	35% (38/109)	23% (16/69)	41% (35/86)	..	24% (11/46)	39% (24/61)	..
1	28% (29/103)	31% (34/109)	32% (22/69)	34% (29/86)	..	37% (17/46)	33% (20/61)	..
2	34% (35/103)	26% (28/109)	32% (22/69)	26% (22/86)	..	26% (12/46)	21% (13/61)	..
3	7% (7/103)	8% (9/109)	13% (9/69)	0% (0/86)	..	13% (6/46)	7% (4/61)	..
Participants with grayscale ≥1	69% (71/103)	65% (71/109)	77% (53/69)	60% (51/86)	..	76% (35/46)	61% (37/61)	..
Participants worsening by 1 point from baseline	..	..	30% (21/69)	20% (17/85)	-10.4% (-24.2 to 3.4)	35% (16/46)	27% (16/60)	-8.1% (-25.9 to 9.6)
Composite outcome	..	..	55% (49/89)	25% (22/88)	-30.1% (-43.8 to -16.3)	66% (53/80)	51% (41/81)	-15.6% (-30.7 to -0.60)
PD maximum score								
0	72% (74/103)	73% (80/109)	62% (43/69)	86% (74/86)	..	78% (36/46)	80% (49/61)	..
1	15% (15/103)	8% (9/109)	16% (11/69)	8% (7/86)	..	11% (5/46)	8% (5/61)	..
2	9% (9/103)	17% (19/109)	22% (15/69)	6% (5/86)	..	9% (4/46)	10% (6/61)	..
3	5% (5/103)	1% (1/109)	0% (0/69)	0% (0/86)	..	2% (1/46)	2% (1/61)	..
Participants with PD ≥1	28% (29/103)	27% (29/109)	38% (26/69)	14% (12/86)	..	22% (10/46)	20% (12/61)	..
Participants worsening by 1 point from baseline	..	..	26% (18/69)	11% (9/85)	-15.5% (-27.8 to -3.2)	15% (7/46)	12% (7/60)	-3.6% (-16.7 to 9.6)
Composite outcome	..	..	52% (46/89)	16% (14/88)	-35.8% (-48.7 to -22.9)	53% (42/80)	42% (34/81)	-10.5% (-25.9 to 4.8)
Combined maximal score (grayscale and PD)								
0	31% (32/103)	33% (36/109)	22% (15/69)	41% (35/86)	..	24% (11/46)	39% (24/61)	..
1	27% (28/103)	28% (31/109)	32% (22/69)	34% (29/86)	..	37% (17/46)	33% (20/61)	..
2	33% (34/103)	29% (32/109)	33% (23/69)	26% (22/86)	..	26% (12/46)	20% (12/61)	..
3	9% (9/103)	9% (10/109)	13% (9/69)	0% (0/86)	..	13% (6/46)	8% (5/61)	..
Participants with combined score ≥1	69% (71/103)	67% (73/109)	78% (54/69)	59% (51/86)	..	76% (35/46)	61% (37/61)	..
Participants worsening by 1 point from baseline	..	..	32% (22/69)	18% (15/85)	-14.2% (-27.9 to -0.6)	35% (16/46)	27% (16/60)	-8.1% (-25.9 to 9.6)
Composite outcome	..	..	56% (50/89)	23% (20/88)	-33.5% (-47.0 to -19.9)	66% (53/80)	51% (41/81)	-15.6% (-30.7 to -0.6)

At each assessment, grayscale and PD scores were recorded for a predefined core set of 24 joints (appendix pp 4-6). Combined scores were generated using the EULAR-OMERACT combined scoring system in which the higher of the two parameters determines the severity grading of synovitis (0, normal synovitis; 1, minimal synovitis; 2, moderate synovitis; 3, severe synovitis). PD=power Doppler.

**Table 3: Comparison between groups of grayscale synovial hypertrophy, power Doppler, and EULAR-OMERACT combined ultrasound scores for grading the severity of synovitis**

[3%] in the abatacept group and one [1%] in the placebo group).

**Discussion**

The results of this phase 2B study indicate that treatment of adults at high risk of developing rheumatoid arthritis with abatacept reduces progression to clinically apparent arthritis during the treatment phase. Even after stopping treatment, the number of events in the abatacept group remained lower than the placebo group, suggesting sustained efficacy. However, by 24 months, the symptom burden, including quality-of-life assessments and pain, as well as ultrasonography of subclinical inflammation, was similar between groups, indicating that the effects of 12 months of abatacept treatment are not sustained.

These findings could be explained by a number of factors. Mechanistically, the data confirm that T-cell costimulation plays a role in the progression from the at-risk state to rheumatoid arthritis, operating systemically and in synovial joints. The trial also provides evidence

that harmful adaptive immune reactions contribute to the symptom burden associated with the at-risk state, as they do in established disease.<sup>8,9</sup> Furthermore, the outcome of treatment withdrawal on the intention-to-treat population suggests that pathogenic immune responses re-emerge and are not modified permanently by a fixed period of costimulation modulation. Another factor that might explain why the effect of abatacept on the symptom burden is not sustained relates to the study design and analysis. In APIPPRA, all eligible participants were encouraged to remain in the study throughout the 24 months, regardless of outcomes. Accordingly, changes in secondary outcomes over time reflect the effects of study intervention as well as disease-modifying antirheumatic drugs and corticosteroids, initiated in those who met the primary endpoint. The APIPPRA pre-specified analysis is distinct from that reported for the TREAT EARLIER<sup>19</sup> and ARIAA trials,<sup>20</sup> summarised below, in which participants were censored from the time of detection of clinical arthritis. By excluding data from

those who met the primary outcome, changes in patient-reported outcomes, such as HAQ, were sustained beyond the treatment period in these studies.

Published literature reporting trials of interception in individuals at risk of rheumatoid arthritis is limited to a few studies. Bos and colleagues showed that in 83 participants positive for ACPA or IgM rheumatoid factor with arthralgia, dexamethasone 100 mg injections at baseline and at 6 weeks reduced autoantibody concentrations by 50%. However, by 24 months, arthritis-free survival curves had fully converged.<sup>21</sup> Among 82 individuals at risk of rheumatoid arthritis in the phase 2b PRAIRI study, progression to rheumatoid arthritis was delayed by about 12 months in those undergoing B-cell depletion with a single 1000 mg intravenous infusion of rituximab. However, the overall risk of developing rheumatoid arthritis was no different from placebo by 48 months of follow-up.<sup>22</sup> In the TREAT EARLIER trial of participants with arthralgia and MRI-detected subclinical joint inflammation, and positive or negative for ACPA, 1 year of methotrexate (with a single intramuscular injection of methylprednisolone) did not prevent onset of rheumatoid arthritis by 24 months.<sup>19</sup> In individuals positive for ACPA with higher rates of progression, methotrexate delayed onset of rheumatoid arthritis. However, there were consistent and sustained improvements in patient-reported outcomes, regardless of ACPA status. The StopRA study, a double-blind, placebo-controlled study of hydroxychloroquine versus placebo enrolling individuals positive for anti-cyclic citrullinated peptide 3 with or without symptoms, is yet to report in full.<sup>23</sup> An interim analysis of 142 eligible participants indicated that the Kaplan–Meier estimated probabilities of developing rheumatoid arthritis were 34% in the hydroxychloroquine group, and 36% in the placebo group; arthritis-free survival curves over 36 months were superimposed.<sup>23</sup>

The ARIAA study aimed to examine whether 6 months of abatacept treatment could reverse subclinical inflammation as measured by MRI in 98 participants positive for ACPA with arthralgia and a positive MRI scan in the dominant hand at baseline.<sup>20</sup> Compared with APIPPRA, dosing was for 6 months versus 12 months and, although symptoms and serology were similar, the study mandated synovial joint inflammation by MRI. The ARIAA results showed improvement in at least one of three parameters (synovitis, tenosynovitis, or osteitis) in 28 (57%) of 49 participants in the abatacept group compared with 15 (31%) of 49 participants in the placebo group at 6 months, effects that were sustained 1 year after stopping treatment. Furthermore, the proportions of individuals progressing to rheumatoid arthritis at 6 months were four (8%) of 49 in the abatacept group and 17 (35%) of 49 in the placebo group and, although differences converged after stopping treatment, they remained significant at the end of study (17 [35%] of 49 vs 28 [57%] of 49).

	Events or participants	Placebo (n=102)	Abatacept (n=109)
All adverse events	1036	475 (46%)	561 (54%)
Participants reporting ≥1 adverse event	191	91 (89%)	100 (92%)
Difference in proportions (95% CI)	..	..	2.5% (-5.4 to 10.5)
Participants reporting ≥1 adverse event classified as infection	119	62 (61%)	57 (52%)
Difference in proportions (95% CI)	..	..	-8.5% (-21.8 to 4.8)
Common adverse events			
Common cold	80	42 (41%)	38 (35%)
Sore throat	37	17 (17%)	20 (18%)
Nausea	27	7 (7%)	20 (18%)
Chest infection	25	19 (19%)	6 (6%)
Headache	25	9 (9%)	16 (15%)
Diarrhoea	24	12 (12%)	12 (11%)
Dental	20	7 (7%)	13 (12%)
Back pain	16	13 (13%)	3 (3%)
Abdominal pain	15	4 (4%)	11 (10%)
Mouth ulcers	12	2 (2%)	10 (9%)
Fatigue	11	5 (5%)	6 (6%)
Most frequent laboratory adverse events			
Anaemia	8	3 (3%)	5 (5%)
Transaminitis (raised ALT or AST)	7	5 (5%)	2 (2%)
Iron deficiency	4	3 (3%)	1 (1%)
Leucopenia	3	1 (1%)	2 (2%)
Hyperlipidaemia	3	1 (1%)	2 (2%)
Folate deficiency	2	1 (1%)	1 (1%)
Leukocytosis	1	0	1 (1%)
Raised creatine kinase	1	1 (1%)	0
Participants reporting ≥1 serious adverse event, including death, IMEs, and SARs	17	11 (11%)	6 (6%)
Difference in proportions (95% CI)	..	..	-5.3% (-12.7 to 2.1)
Serious adverse events			
Death	2	1	1
Infection	3	3	0
Cardiovascular events	3	2	1
Venous thromboembolism	1	1	0
Malignancy	4	1	3
Admission for elective surgery	5	3	2
Pregnancies, events			
Pregnancy	5*	1	4
Pregnancy for partner	2†	0	2
Participants reporting ≥1 adverse event in the laboratory category	29	15 (14.7%)	14 (13%)
Study discontinuation due to adverse events	4	1 (1%)	3 (3%)
Difference in proportions (95% CI)	..	..	1.8% (-1.8 to 5.4)

Descriptive data summarising adverse events, severe adverse events, and IMEs for all participants administered at least one dose of study drug (n=211). There were 20 participants without adverse events (11 in the placebo group and nine in the abatacept group). Common adverse events were defined as those occurring at a frequency of 5% or more. ALT=alanine aminotransferase. AST=aspartate aminotransferase. IMEs=important medical events. SAR=serious adverse reaction. \*One pregnancy was recorded during the treatment period and was terminated early due to reasons unrelated to study treatment. Four pregnancies were recorded outside of the protocol window. One pregnancy was voluntarily terminated; there were no other adverse pregnancy outcomes. †Both pregnancies were recorded during the treatment period.

**Table 4: Safety assessments**

Another feature distinguishing the APIPPRA study from other interception trials is the risk profile of the cohort itself. For example, in TREAT EARLIER and ARIAA, MRI-positive inflammation was mandated for inclusion. This criterion was not a requirement for inclusion in APIPPRA in which most participants had no or low levels of subclinical inflammation by ultrasonography. This lower risk state was also reflected in the treatment and placebo groups in lower scores for tender joint count (median 1 vs 2) and pain (VAS 24 vs 24), which were similar to the PRAIRI study (median tender joint count two vs none),<sup>22</sup> but lower than baseline symptoms reported in the TREAT EARLIER (median tender joint count 68 of four vs three; pain VAS 50 vs 50)<sup>19</sup> and ARIAA trials (median tender joint count two vs three; pain VAS 43 vs 46).<sup>20</sup> These values appear small and the differences modest, but the trends are in keeping with the progression rates in their respective placebo groups, being 67% for participants positive for ACPA with arthralgia in TREAT EARLIER and 57% in ARIAA, compared with 40% in the PRAIRI study and 37% in APIPPRA.<sup>19,20,22</sup> Taken together with baseline ultrasonography, these data suggest that the APIPPRA study population resides in an earlier phase of the risk trajectory, representing a lower risk population in terms of progression over 2 years.

The strengths of the APIPPRA trial are the inclusion of participants positive for ACPA, the fixed-period dosing, the real life clinical setting with opportunistic recruitment from early arthritis clinics, the adoption of a robust primary endpoint confirmed by sonography in which all primary events fulfilled the ACR/EULAR 2010 criteria, the low preprimary event withdrawal rate, and the evaluation of the effects of study drug on subclinical synovitis. Sonography allowed us to establish that many study participants had no or low levels of detectable subclinical synovitis, indicating that the APIPPRA study cohort represents a population with minimal joint involvement. Finally, the results show the positive effect of co-stimulation modulation on the symptom burden of people at risk of rheumatoid arthritis with consistent reductions in symptoms and improvements in patient-reported outcomes across multiple domains.

The limitations of the study include the short follow-up period, leaving the question of delay versus prevention partly unanswered. Long-term follow-up of the trial population, which is ongoing, might address this limitation. Arthritis-free survival curves show that a substantial proportion of individuals in each group do not progress to rheumatoid arthritis, and some of these participants might have been unnecessarily exposed to the study drug. Such exposure raises the importance of risk assessment and highlights the need for improved stratification tools to identify individuals at highest risk of rheumatoid arthritis. Good examples of such tools include the EULAR criteria for clinically suspicious arthralgia that progresses to inflammatory arthritis,<sup>24</sup>

signatures associated with pathogenic adaptive immune responses (ie, autoantibody V domain glycosylation),<sup>25</sup> and features extrapolated from preclinical models.<sup>26</sup> Studying the triggers of rheumatoid arthritis is of paramount importance and will probably uncover pathways directly linked to the risk state. Regarding biomarkers to inform therapeutic options for interception, abatacept should be considered in individuals with high titres of anti-cyclic citrullinated peptide or carrying *HLA-DRB1* shared epitope allomorphs.<sup>11,27</sup>

Another limitation is the assessment choice for capturing clinically meaningful changes in response to the study drug. Although many secondary outcomes improved with the study drug, baseline scores in this at-risk population were low, reflecting a cohort of individuals with a moderately good quality of life but who have a better quality of life with abatacept than placebo. Furthermore, baseline changes might not have achieved minimal clinically important differences, as defined for established rheumatoid arthritis, which might account for the discrepancy between groups for primary endpoints and patient-reported outcomes at 24 months. Our data would suggest that radiography, unlike ultrasonography or MRI, might be of limited value in identifying a group at high risk, or evaluating the effect of disease interception in individuals at risk of rheumatoid arthritis. Although 16% of participants had radiographically detected bone erosions at baseline, most had scores of 1 or less; the presence of erosions at baseline would not appear to be associated with progression to rheumatoid arthritis. Therefore, evaluating minimal disease activity states is challenging,<sup>28</sup> since DAS-28, simple disease activity score, and clinical disease activity score (in which swollen joint counts are included) have not been validated, nor are likely to be appropriate for assessing at-risk states over time. Thus, the APIPPRA study might not have captured all the features associated with progression, especially those symptom complexes considered important to at-risk individuals. We suggest that the development of new or revised outcome measures informed by patient experts, including symptoms such as those identified with the SPARRA questionnaire,<sup>29</sup> should be a priority.

By applying a stringent cutoff of 90% or more injections to define adherence to study medication, 29 participants in the abatacept group and 26 in the placebo group were non-adherent, representing 26% of the intention-to-treat population. Given that the proportion of participants who were non-compliant was similar in both groups (26% for abatacept and 25% for placebo) it seems unlikely that non-adherence was related to study drug. The TREAT EARLIER study offers a trial setting with which to compare rates of non-adherence, because methotrexate was also taken on a weekly basis for 12 months, but in tablet form rather than by injection.<sup>19</sup> By the end of the 12-month treatment period 27% of participants in the methotrexate group and 19% in the placebo group had discontinued all study tablets.<sup>19</sup> The proportion of non-

censored participants discontinuing methotrexate was even higher in those taking methotrexate 20 mg or more weekly when compared with those taking any dose, suggesting that drug intolerance might have been a contributing factor. Regardless, non-adherence in TREAT EARLIER appears similar to levels recorded in the APIPPRA study. The prevalence of adherence to biological therapies in established rheumatoid arthritis was reported to be 64% in the first 6 months of treatment when adopting a less stringent cutoff of more than 80%.<sup>30</sup> By acknowledging that drug adherence might be partly better in clinical trials than in routine clinical practice, non-adherence rates in interception trials reported to date appear similar. These findings might be of value when designing future interception trials.

To conclude, we show the feasibility and acceptability of rheumatoid arthritis interception trials and report data to suggest that co-stimulation modulation during the at-risk phase is well tolerated and substantially reduces signs and symptoms associated with the at-risk state during the treatment period. The data indicate that abatacept treatment beyond 12 months might be required to sustain efficacy over time. Intermittent administration at intervals remains to be assessed. This study highlights the need for criteria that distinguish the at-risk phase from early rheumatoid arthritis to support trial design, while targeting treatment at the most appropriate time. Ultimately, when considering reducing the risk of rheumatoid arthritis with biological therapy dosed over a fixed period, the incremental gains of not requiring a disease-modifying antirheumatic drug over time need to be balanced against the upfront treatment costs and the challenges of predicting individuals at high risk.

#### The APIPPRA study investigators

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#### Contributors

APC was the chief investigator and conceived and designed the study in collaboration with PE, SQ, IBM, JDI, AGP, BAF, CDB, PH, MHB, CC, TH, RT, and ATP. AF and MAD'A supervised ultrasonography training, development of the ultrasound imaging reference atlas, and adjudication and quality checks of ultrasound images. KR and DvS contributed to the study design and development of the SPARRA questionnaire. JCV and ATP planned, undertook, and interpreted the statistical analysis of the data. MJ was the senior trial manager. CM, JK, and EG managed all aspects of Clinical Trials Unit operations. The APIPPRA study investigators contributed to identification and recruitment of at-risk individuals, collection of clinical and imaging data, development of the ultrasonography protocol, interpretation of the data, and review of the final manuscript. APC, MJ, JCV, AF, SQ, MAD'A, and ATP verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

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#### Data sharing

Reasonable requests for data can be submitted to the corresponding author and will be considered on an individual basis.

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