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Summary

Background Clinical trials aimed at preventing rheumatoid arthritis in individuals at risk have had variable results. The long-term outcomes of disease interception, however, are not known. We aimed to examine the long-term effect of therapeutic intervention, with emphasis on efficacy and safety.

Methods The Arthritis Prevention In the Preclinical Phase of Rheumatoid arthritis with Abatacept (APIPPRA) phase 2b, randomised controlled trial recruited 213 anti-citrullinated protein antibody (ACPA) positive individuals with arthralgia in 28 hospital-based early arthritis clinics in the UK and three in the Netherlands, randomly assigning participants to 52 weekly subcutaneous injections of 125 mg abatacept (n=110) or placebo (n=103), with another 52 weeks of follow-up. The APIPPRA Long-Term Outcome (ALTO) study extended follow-up for between 4 and 8 years and study participants and clinical assessors remained masked to treatment group. The primary outcome was the time from randomisation to development of clinical synovitis in at least three joints, rheumatoid arthritis according to American College of Rheumatology–European Alliance of Associations for Rheumatology 2010 criteria, or first treatment with disease modifying anti-rheumatic drugs, whichever was met first. The primary outcome was also stratified by autoantibody profiles defined at the time of randomisation. People with lived experience of rheumatoid arthritis had input into the APIPPRA study design. The study was registered at ISRCTN (ISRCTN-12680338), and is completed.

Findings Between April 26, 2021, and Jan 31, 2023, 143 APIPPRA study participants enrolled in ALTO: 71 in the abatacept group and 72 in the placebo group (mean age 48·2 years [SD 11·2], 112 [78%] females, 31 [22%] males, 116 [81%] White). Median follow-up time from randomisation was 55 months (IQR 23–74). Primary events increased by 54 to 119. The initial between-group difference in restricted mean arthritis-free survival time observed at 2 years in APIPPRA remained significant at 4 years (4·9 months 95% CI 0·1–9·6; p=0·044), although the magnitude of this difference diminished over time. Assessments of disease activity and patient reported outcomes revealed no significant differences between groups beyond the treatment period. However, although participants with a broad autoantibody profile at baseline were at highest risk of progressing, this subgroup responded better to abatacept. There were 18 serious adverse events in the abatacept group and 13 in the placebo group; none deemed related to study drug.

Interpretation In this at-risk population, 1-year treatment with abatacept delayed progression to rheumatoid arthritis for up to 4 years. Those at highest risk of progression have a broad autoantibody profile but are more responsive to abatacept treatment.

Funding Bristol Myers Squibb.

Lancet Rheumatol 2026; 8: e171–80

Published Online January 20, 2026 https://doi.org/10.1016/S2665-9913(25)00371-6

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Introduction

Rheumatoid arthritis is a chronic immune-mediated inflammatory disease characterised by substantial physical, mental, and societal burden.[1,2] This is especially the case for more severe, autoantibody positive erosive rheumatoid arthritis, whereby patients can cycle through disease modifying drugs to the point of becoming treatment-refractory.[3] This has motivated attempts to embrace a so-called predict and prevent paradigm, underpinned by risk stratification and associated rates of progression to rheumatoid arthritis.[4,5]

The detection of anti-citrullinated protein antibodies (ACPA), coupled with inflammatory joint pain with or without subclinical inflammation, has defined a phenotype of individuals at risk of rheumatoid arthritis for randomised clinical trials seeking to delay or prevent the onset of disease.[6–8] This approach has been met with some success with studies, including APIPPRA, showing evidence of delay depending on the intervention and target population.[9–14] However, challenges remain with uncertainties around the durability of treatment, identification of individuals at highest risk of progression

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See Online for appendix

Research in context

Evidence before this study

Clinical phenotypes of individuals at high risk of developing rheumatoid arthritis have emerged from studies of inception cohorts reported in the early 2000s. Since that time, efforts have focused on capturing rates of progression and refining risk stratification to inform the design and sample size calculations for randomised controlled trials of rheumatoid arthritis prevention, now termed disease interception. Literature searches in PubMed, Embase, Cochraine Library, as well as clinical trial registries up until Aug 31, 2025 have uncovered several randomised controlled trials of rheumatoid arthritis disease interception. Experience to date has been reviewed recently by Deane and colleagues, encompassing six completed trials of fixed period dosing of corticosteroids, rituximab (the PRAIRI study), methotrexate (TREAT EARLIER), abatacept (APIPPRA and ARIAA trials) and hydroxychloroquine (STOP-RA), with variable results. The APIPPRA study was conceived and designed in 2013. The first study participant enrolled in January, 2015, and the results of the trial published in 2024. Together with ARIAA, the results indicate that up to 12 months treatment with abatacept reduces rates of progression to rheumatoid arthritis and significantly reduces the symptom burden. In the APIPPRA study, arthritis-free survival curves converge after stopping treatment, but at 24 months the survival curves have not merged. These data highlighted the need for longer term follow-up to capture arthritis-free survival over more extended periods of time and the durability of the intervention, as well as long-term safety profiles.

Added value of this study

Here, we present the results of a long-term follow-up study in which we have captured data on those originally randomly assigned to the APIPPRA study. The results show that abatacept reduces the symptom burden and prevents progression to rheumatoid arthritis during the treatment period, while delaying disease onset for up to 4 years. A high-risk group is defined, based on high titres of anti-citrullinated protein autoantibody and an extended autoantibody serotype, indicative of a more mature autoimmune response. These individuals are more likely to progress to rheumatoid arthritis but are also more responsive to abatacept treatment. 1-year treatment of at-risk individuals with abatacept is well tolerated; the trial did not reveal any untoward safety signals after extended follow-up.

Implications of all the evidence

The ALTO study shows the importance of long-term follow-up for capturing primary endpoints as well as safety data, and to establish the durability of therapeutic intervention in individuals at risk of rheumatoid arthritis. The proportion of individuals who remained arthritis-free in the trial highlights the need to better refine risk stratification.

and those most likely to respond to the intervention, and capturing outcome and safety data over more extended periods of time. Given these challenges, we carried out a long-term follow-up study of the APIPPRA trial to better understand progressor and responder phenotypes, and to establish the true effect of disease interception.

Methods

Study design and participants

APIPPRA was a phase 2b, randomised, double blind, placebo-controlled trial of individuals at risk of developing rheumatoid arthritis.[13,15] Adults aged 18 years or over, had inflammatory arthralgia without clinical synovitis, and were positive for serum autoantibodies associated with a high-risk state (either ACPA and rheumatoid factor positive or with high ACPA titres without rheumatoid factor). All study participants who had completed the APIPPRA trial were invited to participate in the ALTO follow-up study, regardless of whether they had met the primary endpoint in the APIPPRA study (London South East Research Ethics Committee reference 21/LO/0035), to address the effect of interception on safety and longer-term disease trajectories. The objectives of the follow-up period were to identify those individuals progressing to rheumatoid arthritis beyond the APIPPRA period, to explore the durability of the intervention both in terms of the primary endpoint and the symptom burden, and to evaluate long-term safety. Participants who never received study drug were excluded (appendix p 30). Participants provided written informed consent before their first visit and were followed up 6-monthly until Jan 31, 2023. Study oversight was provided by independent trial steering and data monitoring committees. Input into the APIPPRA study design, shaping of the research questions, and assessment of the burden of intervention was provided by a patient research partner focus group, which included members of the National Rheumatoid Arthritis Society. The study was registered at ISRCTN (ISRCTN-12680338) and is completed.

Randomisation and masking

In APIPPRA, participants were randomly assigned to receive 52 weekly subcutaneous injections of placebo (n=103) or 125 mg abatacept (n=110) using computer-generated randomisation and followed up for a further 52 weeks after stopping treatment.[13,15] Although the ALTO study was a follow-up study requiring no additional study intervention, study participants and clinical assessors remained masked to treatment group.

Outcomes

In APIPPRA, the primary endpoint was the time to development of clinical synovitis or rheumatoid arthritis

according to one of two methods: time to development of clinically apparent synovitis in at least three joints, or the time to development of rheumatoid arthritis according to the American College of Rheumatology–European Alliance of Associations for Rheumatology (ACR–EULAR) 2010 criteria,[16] whichever was met first.[13] For those participants meeting the endpoint during APIPPRA this was their ALTO primary endpoint. A third event, the time to first treatment with a disease-modifying antirheumatic drug (DMARD) was included to permit precise capture of events both retrospectively from medical records in the intervening period between studies, and prospectively at ALTO study visits. Corticosteroids were excluded from this third event to take account of treatment for non-arthritic indications. In APIPPRA, a small number of participants initiated DMARDs despite these being classified as forbidden medication. For these participants, the first date after the end of the APIPPRA period constituted the primary endpoint (appendix p 63). The primary endpoint, censored at 6 years, was the time from randomisation to development of whichever of these three events was met first. All other efficacy outcomes were acquired prospectively at scheduled ALTO study visits.

Clinical assessments of efficacy included disease activity score in 28 joints (DAS28; 28 tender and swollen joint counts, patient global visual analogue score [VAS], erythrocyte sedimentation rate [ESR]), Extended Joint Count 68/66, Simple Disease Activity Score and Clinical Disease Activity Score, Pain VAS, Health Assessment Questionnaire and Euro-Quality of Life Questionnaire (EQ-5D-3L). Additional endpoints were the time to and proportion of participants requiring conventional synthetic DMARD therapy, or oral or parenteral corticosteroids for the treatment of inflammatory arthritis, and the time to commencing biological DMARD therapy. In contrast to APIPPRA, imaging assessments for the development of rheumatoid arthritis by ultrasound were not mandated in the ALTO study protocol and are not reported here. Progression of erosions and joint space narrowing in x-rays of the hands and feet between the APIPPRA baseline visit and the ALTO study final visit were defined by the van der Heijde Sharp modified method,[17] scored by two independent readers in time order.

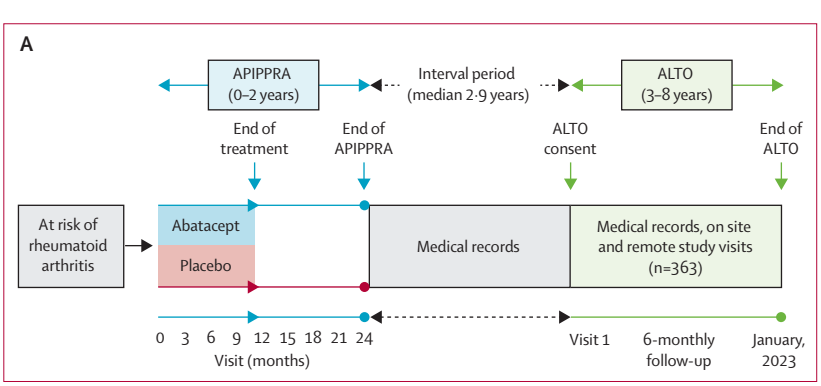
Assessment of safety focused on severe adverse events and events of special interest, including cardiovascular events, infections, and cancer. These events were also collected retrospectively from medical records to cover the intervening period between APIPPRA and ALTO. Since participants had not received study drug for at least 12 months before enrolling in ALTO, non-serious adverse events were not recorded.

In exploratory analyses aimed at stratifying outcomes according to baseline autoantibody profiles, as specified in the ALTO study protocol, serum autoantibody profiles were analysed by a centralised laboratory (Leiden University Medical Centre, the Netherlands) for the presence of IgG and IgA ACPA, anti-carbamylated protein antibodies and anti-acetylated protein autoantibodies, as previously described.[18,19] Clinical laboratory values acquired by recruiting centres were used to define rheumatoid factor status. The upper limit of detection in the IgG ACPA assay is at least 340 international units (IU)/mL. The detection of all five serum autoantibodies (rheumatoid factor, IgG ACPA, IgA ACPA, anti-carbamylated protein antibodies, and anti-acetylated protein autoantibodies), regardless of antibody titre, was designated an extended serotype, reflecting a more mature autoimmune response.

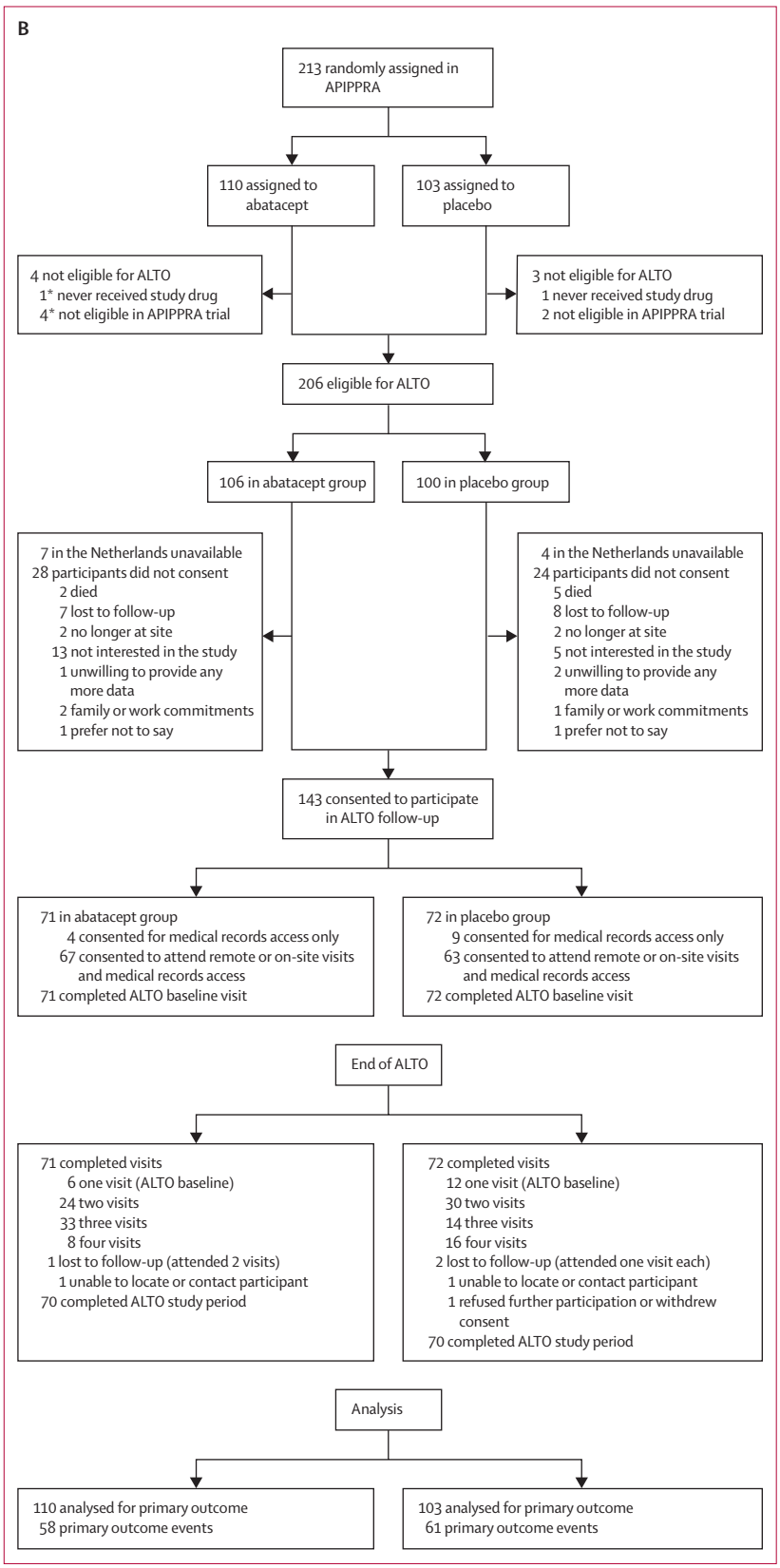
Statistical analysis

The APIPPRA trial provided 80% power to detect a 50% reduction in arthritis development over 2 years from 40% to 20% (hazard ratio [HR] 0·437). This required 52 events from 172 participants; 213 were randomly assigned to allow for dropout. All eligible APIPPRA participants were invited to enrol in ALTO and with the further follow-up, power was assessed to be maintained to detect this effect over the longer term (appendix p 57).

Analysis of the primary outcome and other time-to-event outcomes, including prespecified exploratory analysis of outcomes stratified by baseline autoantibody status, were carried out by estimating Kaplan–Meier survival curves for each study group to assess timing of their convergence to a common incidence, and by estimating the between-group difference in restricted mean survival time (mean delay in incidence with 95% CI).[20] HRs were not reported as they varied through time during the APIPPRA period and the proportional hazards assumption was not met.[13] For the purpose of analysing continuous secondary repeated-measures outcomes, the timing of each data value was categorised to be centred at 6-month intervals from randomisation with a 3-month window. Each participant could have at most one value per timepoint, being the closest datapoint. A linear mixed effects model of the change from baseline incorporated a random intercept for subject, auto-regressive correlation structure between timepoints, and main effects for time and study group and their



(Figure 1 continues on next page)



interaction. The area under curve (AUC) in each group was derived from the model's estimates and covariances of the effect of time on outcome over the 36–84-month period and then divided by the time range to be interpretable back on the original outcome scale. These provided, for each outcome, the between-group difference in the AUC during ALTO from 3 to 7 years, with its 95% CI. These were also presented as standardised effect sizes to aid judgement of clinical significance. Longitudinal effects were illustrated additionally by use of smoother polynomial curves to aid interpretation. The SPSS Statistics package was used for this analysis.

Role of the funding source

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

Results

Between April 26, 2021 and Jan 31, 2023, 143 of 213 participants randomly assigned in the APIPPRA trial consented to follow up in ALTO, 71 from the abatacept group and 72 from the placebo group (figure 1). Mean age was 48·2 years (SD 11·2), 112 (78%) of 143 were females, 31 (22%) were males, and 116 (81%) were White. At enrolment, health records were interrogated retrospectively for all 143 participants to capture primary outcomes and safety data in the intervening period between the end of APIPPRA and the beginning of ALTO (median interval of 2·9 years, IQR 1·7–4·0). Collectively, participants attended 363 study visits during the ALTO study period until the end of the study (figure 1). Median follow-up time from randomisation was 55 months (IQR 23–74; mean 50 months). A comparison of the baseline characteristics of the APIPPRA and ALTO participants is summarised in table 1 and the appendix (p 4). For the primary survival analysis, in addition to the 213 randomly assigned participants providing up to 2 years of follow-up time and events during APIPPRA, 143 participants had extended followed up in ALTO, of whom 45 had already met the primary endpoint in APIPPRA. 20 of the 70 participants not enrolling in ALTO had already met the primary endpoint, and 50 participants were censored after contributing in APIPPRA (appendix p 4).

The primary endpoint result is shown in figure 2A. Estimates from the Kaplan–Meier survival plot, accounting for withdrawals, indicated that the cumulative numbers of primary events were 42 for abatacept versus 51 for placebo at 3 years, 48 versus 56 at 4 years, and 51 versus 59 at 5 years (appendix p 4). This translates

Figure 1: **Schematic of the APIPPRA and ALTO study periods (A) and CONSORT diagram (B)**
ALTO=APIPPRA Long-Term Outcome. APIPPRA=Arthritis Prevention In the Preclinical Phase of Rheumatoid arthritis with Abatacept. *One was ineligible for both reasons.

to cumulative proportions progressing to rheumatoid arthritis of 50% for abatacept versus 54% for placebo at 3 years, 59% versus 61% at 4 years, and 64% versus 65% at 5 years. By 6 years the proportions progressing were 73% with abatacept (55 events) versus 70% with placebo (61 events), with just three further events in the abatacept group after year 6, bringing the total number of events to 119 spanning the APIPPRA and ALTO periods. Of note, all primary endpoints acquired during both APIPPRA and ALTO study visits met the ACR–EULAR 2010 criteria. During the interval between APIPPRA and ALTO there were 42 participants meeting the endpoint of time to first DMARD. If these endpoints also met ACR–EULAR 2010 criteria is not known. The restricted mean survival times after 4 years of follow-up were 34·0 months (SE 1·6) in the abatacept group and 29·1 months (1·9) in the placebo group, with a difference of 4·9 months (95% CI 0·1–9·6; p=0·044), indicating a significant delay in arthritis development, and longer than the 2-year difference of 3·2 months (1·2–5·1) estimated in APIPPRA (appendix p 4). The Kaplan–Meier survival curves converged after 4 years, with a pooled estimate of 60% arthritis incidence, indicating delay but not long-term prevention of arthritis.

In APIPPRA, 12 participants initiated DMARDs despite these being classified as forbidden medication. For comparability with the ALTO follow-up study, where DMARD initiation, including corticosteroids, constitutes the primary endpoint, we recoded these APIPPRA participants as having met the endpoint at the first date after the end of the APIPPRA period. To align primary endpoints across both APIPPRA and ALTO periods we undertook sensitivity analysis and applied the ALTO study endpoint definition to the APIPPRA period, which included time to first DMARD. Kaplan–Meier plots and respective arthritis-free proportions are shown in the appendix (pp 5–6). Differences in restricted mean survival time in months between groups were 5·3 (95% CI 1·9 to 8·7) after 3 years, 6·0 (1·1 to 10·9) after 4 years, 6·3 (–0·01 to 12·7) after 5 years, and 6·5 (–0·3 to 14·3) after 6 years in favour of abatacept.

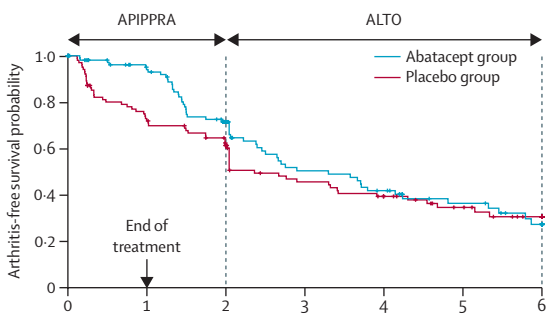
In prespecified exploratory analysis, outcomes according to baseline autoantibody profiles were evaluated following re-assay of IgG ACPA levels in all serum samples and adopting titres of at least 340 IU/mL to define high ACPA status. We identified 81 participants with ACPA titres of at least 340 IU/mL at baseline. When compared with the overall population, the difference between groups in the cumulative arthritis-free proportions at 2 years was greater in high ACPA participants (73% in the abatacept group *vs* 51% in the placebo group; figure 2B). By 4 years cumulative arthritis-free proportions were 41% for abatacept and 33% for placebo. For those with ACPA titres of less than 340 IU/mL, cumulative arthritis-free proportions were similar between groups by 18 months (figure 2C). We also compared outcomes in 50 individuals testing positive in all five autoantibody assays including rheumatoid factor, IgG ACPA, IgA ACPA, antibodies to acetylated protein antigens, and antibodies to carbamylated protein antigens with those with less than five assays testing positive, irrespective of antibody concentrations. Although this extended autoantibody serotype was associated with higher rates of progression to arthritis in the placebo group, especially over the first 12-month period, the therapeutic benefit of abatacept was disproportionately increased, sustained beyond the treatment period, and associated with greater separation of arthritis-free survival curves at 2 years (figure 2D). In those with an extended autoantibody serotype, the cumulative arthritis-free proportions were 88% for abatacept and 47% for placebo after 2 years, and 53% for abatacept and 33% for placebo by the end of 4 years of follow-up. For those with the extended serotype, differences between groups were sustained to 6 years, whereas the event rates for those individuals with less than five serotypes were similar by 18 months of follow-up (figure 2E). Comparisons of restricted mean survival times in months are summarised in the appendix (p 6).

	All randomly assigned (n=213)			Followed up in ALTO (n=143)		
	Abatacept n=110	Placebo n=103	Total n=213	Abatacept n=71	Placebo n=72	Total n=143
Age, years	48·3 (11·6)	48·8 (10·9)	48·5 (11·2)	47·2 (12·6)	49·1 (9·5)	48·2 (11·2)
Sex						
Male	26 (24%)	22 (21%)	48 (23%)	17 (24%)	14 (19%)	31 (22%)
Female	84 (76%)	81 (79%)	165 (77%)	54 (76%)	58 (81%)	112 (78%)
Ethnicity						
White	89 (81%)	85 (83%)	174 (82%)	55 (77%)	61 (85%)	116 (81%)
Mixed	3 (3%)	2 (2%)	5 (2%)	3 (4%)	1 (1%)	4 (3%)
Asian	11 (10%)	9 (9%)	20 (9%)	9 (13%)	6 (8%)	15 (10%)
Black	7 (6%)	6 (6%)	13 (6%)	4 (6%)	4 (6%)	8 (6%)
Other	0	1 (1%)	1 (<1%)	0	0	0
Smoking						
Current	21 (19%)	21 (20%)	42 (20%)	8 (11%)	15 (21%)	23 (16%)
Previous	44 (40%)	47 (46%)	91 (43%)	32 (45%)	31 (43%)	63 (44%)
Never	45 (41%)	35 (34%)	80 (38%)	31 (44%)	26 (36%)	57 (40%)
IgG ACPA						
≥340 IU/mL	41 (37%)	40 (39%)	81 (38%)	28 (39%)	29 (40%)	57 (40%)
<340 IU/mL	69 (63%)	63 (61%)	132 (62%)	43 (61%)	43 (60%)	86 (60%)
Serotypes*						
5	23 (21%)	27 (26%)	50 (23%)	13 (18%)	19 (26%)	32 (22%)
<5	87 (79%)	76 (74%)	163 (77%)	58 (82%)	53 (74%)	111 (78%)
Primary endpoint during APIPPRA						
Yes	27 (25%)	38 (37%)	65 (31%)	22 (31%)	23 (32%)	45 (31%)
No	83 (75%)	65 (63%)	148 (69%)	49 (69%)	49 (68%)	98 (69%)

Data are mean (SD) or n (%). ACPA=anti-citrullinated protein autoantibodies. ALTO=APIPPRA. Long-Term Outcome. APIPPRA=arthritis prevention in the pre-clinical phase of rheumatoid arthritis with abatacept. *The five serotypes include rheumatoid factor, IgG ACPA, IgA ACPA, antibodies to acetylated protein antigens, and antibodies to carbamylated protein antigens.

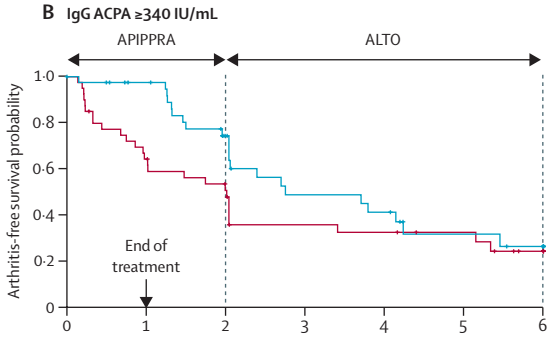
Table 1: **Baseline characteristics comparing those in APIPPRA with those followed up in ALTO by group**

A



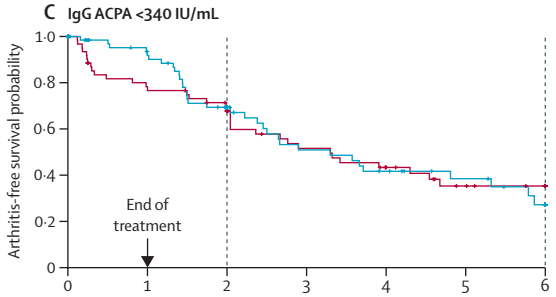
Number at risk (cumulative number of events)							
Abatacept group	110	89	54	35	28	18	..
	(..)	(6)	(27)	(42)	(48)	(51)	(55)
Placebo group	103	69	54	36	28	19	..
	(..)	(29)	(38)	(51)	(56)	(59)	(61)

B IgG ACPA ≥340 IU/mL



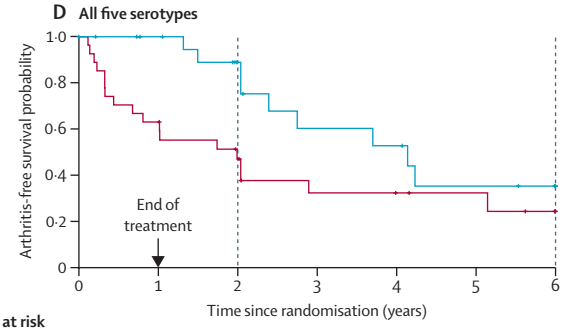
Number at risk (cumulative number of events)							
Abatacept group	41	35	22	13	11	6	..
	..	(1)	(9)	(16)	(18)	(20)	(21)
Cumulative surviving, %	..	97%	73%	49%	41%	33%	27%
Placebo group	40	25	18	11	10	8	..
	..	(14)	(19)	(24)	(25)	(25)	(27)
Cumulative surviving, %	..	65%	51%	36%	33%	33%	23%

C IgG ACPA <340 IU/mL



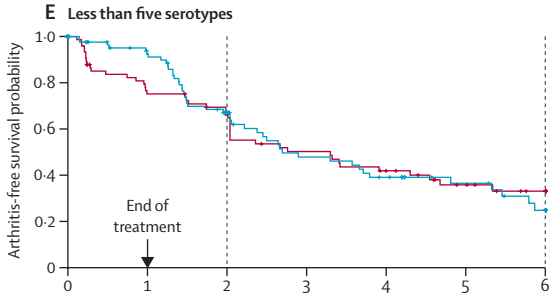
Number at risk (cumulative number of events)							
Abatacept group	69	54	32	22	17	12	..
	..	(5)	(18)	(26)	(30)	(31)	(34)
Cumulative surviving, %	..	92%	68%	50%	41%	38%	27%
Placebo group	63	45	36	25	18	11	..
	..	(14)	(45)	(27)	(31)	(34)	(34)
Cumulative surviving, %	..	77%	68%	52%	43%	35%	35%

D All five serotypes



Number at risk (cumulative number of events)							
Abatacept group	23	19	13	8	7	4	..
	..	(0)	(2)	(6)	(7)	(9)	(9)
Cumulative surviving, %	..	100%	88%	60%	53%	36%	36%
Placebo group	27	17	11	6	5	4	..
	..	(10)	(14)	(17)	(17)	(17)	(18)
Cumulative surviving, %	..	63%	47%	33%	33%	33%	24%

E Less than five serotypes



Number at risk (cumulative number of events)							
Abatacept group	87	70	41	27	21	14	..
	..	(6)	(25)	(36)	(41)	(42)	(46)
Cumulative surviving, %	..	93%	66%	47%	38%	36%	25%
Placebo group	76	53	43	30	23	15	..
	..	(18)	(24)	(34)	(39)	(42)	(43)
Cumulative surviving, %	..	76%	67%	51%	42%	36%	33%

Figure 2: **Kaplan–Meier arthritis-free survival plots for the intention-to-treat population and stratified by baseline serum autoantibody profiles**
Plots compare the arthritis-free survival over time by group for at-risk individuals in (A) the intention-to-treat population, and in those with (B) IgG ACPA ≥340 IU/mL, (C) IgG ACPA <340 IU/mL, (D) five serotypes or (E) less than five serotypes. ACPA=anti-citrullinated protein autoantibodies. ALTO=APIPPRA Long-Term Outcome. APIPPRA=Arthritis Prevention In the Preclinical Phase of Rheumatoid arthritis with Abatacept. Cumulative numbers of events for the end of each interval are shown in parenthes.

We previously reported that abatacept reduces the symptom burden of at-risk individuals during the treatment period, however, 12 months after stopping treatment assessments of disease activity such as tender joint count, pain, Health Assessment Questionnaire, and EQ-5D were similar between groups.[13] In keeping with these findings, analysis of multiple disease activity assessments for up to 7 years of follow-up showed no significant differences between groups (table 2; appendix p 7). For the time to conventional synthetic DMARD treatment or oral or parenteral corticosteroids, the Kaplan–Meier estimated proportions were 39% in the abatacept group and 46% in the placebo group by 2 years. The separation of survival curves between groups is less apparent at the 2-year timepoint, and from 3 years onwards, the proportions were similar in each group (see appendix pp 8–9). By the end of follow-up, 25 participants had received biological DMARDs, 12 in the placebo group and 13 in the abatacept group (appendix pp 8–9).

X-rays of hands and feet were acquired from 105 study participants at their final ALTO study visit (55 in the abatacept group and 50 in the placebo group), and erosion and joint space narrowing scores compared with those acquired at randomisation. x-ray scores were very low, ranging from 0 to 4·7 for erosions, and 0 to 3·03 for joint space narrowing. Overall, 42 (76%) of 55 in the abatacept group and 35 (70%) of 50 in the placebo group had erosion scores of zero, with 45 (82%) of 55 showing no change from baseline erosion scores in the abatacept group and 39 (78%) of 50 showing no change from baseline erosion scores in the placebo group (appendix p 10). For joint space narrowing, 84% in the abatacept group and 72% in the placebo group had scores of zero, and 50 (91%) of 55 in the abatacept group and 44 (88% of 50 in the placebo group showed no change from baseline scores (appendix p 10). Radiographic scores were too low to detect a difference between groups in the proportion of participants with an increase in erosion or joint space narrowing (appendix p 11).

During the combined APIPPRA and ALTO study periods, but excluding the interval in between, there were 18 serious adverse events reported for 15 participants in the abatacept group (15 [14%] of 110) and 13 serious adverse events for 12 participants in the placebo group (12 [12%] of 103); none were deemed related to study drug (table 3). There were 95 events of special interest, excluding two serious adverse events, recorded for 53 participants, 28 in the abatacept group, and 25 in the placebo group. These included seven cancers (two abatacept, five placebo), eight cardiovascular events (three abatacept, five placebo), 58 infections (32 abatacept, 26 placebo), nine pregnancies (five abatacept, four placebo) and one recorded as pulmonary sarcoidosis in the abatacept group. The majority of events were considered mild and unlikely to be related to study drug, with the exception of a nail fungal infection, deemed possibly related to abatacept.

Discussion

The results of the ALTO study highlight the value of long-term follow-up of interventions in individuals at risk

	Mean (SE) AUC† abatacept	Mean (SE) AUC† placebo	Difference‡ (95% CI)	Corresponding standardised effect size (95% CI)§
Disease activity score in 28 joints	−0·01 (0·12)	0·00 (0·12)	−0·01 (−0·34 to 0·33)	−0·01 (−0·29 to 0·28)
Tender joint count of 68 joints	0·7 (0·9)	−1·6 (0·9)	2·3 (−0·2 to 4·8)	0·2 (−0·02 to 0·5)
Swollen joint count of 66 joints	1·6 (0·3)	2·1 (0·3)	−0·5 (−1·3 to 0·3)	−0·4 (−0·9 to 0·2)
Simple Disease Activity Index	1·2 (0·8)	0·0 (0·9)	1·2 (−1·2 to 3·6)	0·2 (−0·2 to 0·5)
Clinical Disease Activity Index	1·3 (0·8)	0·0 (0·9)	1·3 (−1·0 to 3·6)	0·2 (−0·1 to 0·5)
Pain VAS (range 0 to 100 mm)	−1·4 (2·3)	−3·1 (2·4)	1·7 (−4·7 to 8·1)	0·1 (−0·2 to 0·4)
EQ-5D index (range −0·3 to 1)	0·050 (0·015)	0·023 (0·015)	0·027 (−0·009 to 0·063)	0·155 (−0·049 to 0·359)
EQ-5D VAS (range 0 to 100)	4·1 (2·2)	2·3 (2·3)	1·8 (−4·4 to 8·0)	0·1 (−0·2 to 0·4)
Health Assessment Questionnaire-Disability Index (range 0 to 3)	0·05 (0·05)	0·11 (0·05)	−0·05 (−0·19 to 0·08)	−0·08 (−0·27 to 0·12)
Health Assessment Questionnaire-VAS pain (range 0 to 100)	0·1 (2·5)	−2·3 (2·6)	2·3 (−4·7 to 9·3)	0·1 (−0·2 to 0·3)

AUC=area under curve. VAS=visual analogue score. *For all measures, except for the EQ-5D index and EQ-5D VAS, a higher score is indicative of a worse outcome. †AUC of the change from baseline of the outcome over time, obtained from the linear mixed effects model. It is divided by the time range to be on the same scale and units as the outcome measure. ‡Difference between groups (abatacept–placebo) in the AUC. §The widths of the confidence intervals have not been adjusted for multiplicity and ought not to be used in place of hypothesis testing. This column is obtained by dividing the effect by the SD at baseline, except for swollen joints which uses the control group at 24 months. In terms of magnitude (ie, without sign), values of 0·2–0·5 are considered small, values of 0·5–0·8 are considered medium, and values greater than 0·8 are considered large.

Table 2: **Secondary outcomes* compared between groups over years 3–7**

	Abatacept	Placebo
APIPPRA serious adverse events	Death of patient due to bronchopneumonia; adenocarcinoma of the lung*; endometrial cancer*; hysterectomy*; nodular melanoma; right knee replacement; syncope vasovagal*; pregnancy (n=4; *for one of them); pregnancy for partner (n=2 but in same participant)	Death shortly after ascent of Everest*; acute cholecystitis*; chest pain (ruled out unstable angina and pulmonary embolism)*; elective left total knee replacement; ischaemic heart disease—triple vessel coronary artery disease*; left shoulder replacement surgery*; multifocal recurrence of urothelial cancer*; pulmonary embolus right lung; septic tenosynovitis*; total knee replacement for osteoarthritis*; viral infection; pregnancy
ALTO serious adverse events	Right total wrist fusion with partial denervation; extensor carpi ulnaris tenosynovectomy and distal radial ulnar joint synovectomy*; appendicectomy*; uncontrolled hypertension†; allergic reaction to ondansetron; breast cancer*†	Left knee arthroscopy plus partial meniscectomy
Number of ALTO events of special interest by body system		
Respiratory	17	15
Genitourinary	9	10
Cardiovascular	3	5
Gastrointestinal	6	2
Dermatological	5	0
Musculoskeletal	0	3
Haematological	1	2
Eye, ear, nose, and throat	3	0
Neoplasia	0	1
Endocrine	1	0
Immunological	0	1
Pregnancies	5	4
Other	1 (dental infection)	1 (abscess)
Total number of events of special interest	51	44
Total number of participants with at least one event of special interest	28	25

ALTO=APIPPRA Long-Term Outcome. APIPPRA=Arthritis Prevention in the Pre-clinical Phase of Rheumatoid Arthritis with Abatacept. *Severe serious adverse events. †These were also classified as events of special interest.

Table 3: **Safety—serious adverse events and events of special interest**

of developing rheumatoid arthritis, providing evidence for treatment of symptoms and prevention of progression to rheumatoid arthritis when on abatacept, and delay for up to 3 years beyond the 12-month treatment period. At the end of APIPPRA, progression to rheumatoid arthritis in the placebo group was 30%. By the end of the fourth year of follow-up almost 60% of those randomly assigned to placebo had progressed to rheumatoid arthritis, by which point the annual event rate was very low. This study has also uncovered risk strata according to autoantibody profiles, where high baseline IgG ACPA titres or an extended serotype indicative of a broader range of autoantigenic responses are associated with higher rates of progression, with rates of around 50% in the placebo group at 2 years and 77% by the end of follow-up. Notable was the observation that these high-risk individuals also appear more sensitive to T-cell co-stimulation modulation with abatacept, with differences in arthritis-free survival sustained up to 6 years when compared with placebo. These data provide evidence of durability of co-stimulation modulation in participants at highest risk who carry this high-risk autoantibody profile. Nonetheless, there remains a subset of individuals who do not progress, regardless of intervention. Further mechanistic studies are required to explore whether the determinants of progression could be explained further by differences in the burden of effector T-cell subsets that drive the autoimmune response,[21] or by distinctive features of IgG ACPA, such as Fab IgG V-domain glycosylation, as suggested previously.[22]

Although the effects of abatacept on progression to disease were observed up to year 4, the data show that, after stopping treatment, abatacept delays but does not prevent rheumatoid arthritis. Indeed, the benefit of study drug on patient reported outcomes was short-lived and confined to the treatment period, indicating that continuous treatment is required to suppress symptoms such as fatigue, pain, and impaired physical and mental wellbeing. This outcome suggests that adaptive immune responses underpin symptom complexes associated with the at-risk state. Applying disease activity assessments validated for established rheumatoid arthritis revealed low scores and modest effect sizes for study drug. Likewise, low erosion

and joint space narrowing scores, while reassuring, precluded meaningful analysis of any long-term benefit of abatacept based on radiographic changes alone. These findings highlight the need to develop more sensitive assessment tools that capture the disease burden of at-risk individuals, as well as the response to intervention.[23]

Although a strength of the ALTO study was the length of follow-up, and the evenly balanced demographic of the 143 participants across groups, a major limitation was the gap in time between the end of APIPPRA and the recruitment to ALTO for many participants, during which period primary endpoints could not be precisely ascertained. We also failed to enrol all APIPPRA study participants, although some of those not participating had previously contributed primary events. The set-up of new clinical trials was suspended in the UK during the COVID-19 pandemic, such that enrolling participants in the ALTO study once they had completed their last APIPPRA study visit was not permitted. Access to medical records resolved this limitation, permitting precise capture of events during the intervening period, including the initiation of DMARD therapy for the treatment of rheumatoid arthritis. Nonetheless, remote consultations and reluctance to attend hospital clinic centres during this period might have had an effect on clinical and imaging assessments between years 2 and 3.

The ALTO study highlights that, even at the end of 6 years of follow-up, 29% of all at-risk individuals enrolled in the APIPPRA trial had not progressed to rheumatoid arthritis, supporting initiatives to refine the at-risk state with more precision. Recent risk stratification efforts are welcome, including those that couple clinical, imaging, and laboratory factors.[24,25] In depth studies of individuals at risk of rheumatoid arthritis should also uncover a wider range of therapeutic targets extending beyond the existing armamentarium of disease modifying therapies used to treat established rheumatoid arthritis.[5]

Contributors

APC was the chief investigator and conceived and designed the study in collaboration with PE, KM, SQ, IBM, SS, JDI, AGP, BAF, CDB, KR, DvS, AF, MAD'A, PH, MHB, CC, TWJH, REMT, and ATP. AF and MAD'A supervised ultrasound training, development of the US imaging reference atlas, and adjudication and quality checks of US images during the APIPPRA period of the study. KAvS, TWJH, and REMT supervised the autoantibody profiling and SQ and JCV analysed the data. JCV and ATP planned, undertook, and interpreted statistical analysis of the data. MJ was the senior trial manager, and CM, JK, and EG managed all aspects of Clinical Trials Unit operations. All authors had full access to study data, contributing to interpretation and writing of the manuscript, approving final review and submission of the study for publication. APC and ATP directly assessed and verified the underlying data reported in the manuscript.

Declaration of interests

APC was the recipient of an Investigator Sponsored Research grant from Bristol Myers Squibb to fund the APIPPRA study, administered through King's College London. APC, MJ, SQ, MAD'A, BAF, PE, IBM, REMT, KR, and TWJH have received grant funding, consulting or speaker bureau fees, or have been beneficiaries of APIPPRA study funding from Bristol-Myers Squibb in the last 5 years. APC reports consultancy fees from AnaptysBio, BMS, CueBiosciences, Janssen, Medicxi, Lilly, Nucleome Therapeutics, Quell; honoraria from Lilly, Janssen; and participation on an advisory board for Galvani–GSK. AF reports grant funding from Johnson & Johnson, and Synact; and consultancy fees from Johnson & Johnson and Quell Therapeutics. IBM reports grant funding and consultancy fees from AbbVie, Amgen, BMS, Causeway Therapeutics, Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi Regeneron, UCB Pharma, Compugen, AstraZeneca, Moonlake, Dextera, and Pioneering Medicines. SS reports grant funding from Eli Lilly, GSK, Johnson & Johnson (Janssen), Pfizer, and UCB; consultancy fees from AbbVie, AstraZeneca, Johnson & Johnson (Janssen), Syncona, Teijin Pharma, and UCB; honoraria from AbbVie, Amgen, Johnson & Johnson (Janssen), Novartis, Pfizer, and UCB; and support for attending meetings or travel from Johnson & Johnson (Janssen), Pfizer, and UCB. JDI reports grant funding from Pfizer, Janssen, and GSK; consultancy fees from AbbVie, BMS, AstraZeneca Eli Lilly, Roche, AnaptsyBio, Ono Pharma, Quell Therapeutics, and Sonoma; honoraria from AbbVie; and support for attending meetings or travel from Eli Lilly and Gilead. AGP reports research support from GSK, Pfizer, and Gilead; and royalties or licenses from Inflection Biosciences. BAF reports grant funding from Johnson & Johnson, Servier, Galapagos, Celgene, and Novartis; consultancy fees from Novartis, Roche, BMS, Johnson & Johnson, Servier, UCB, Sanofi, Galapagos, AstraZeneca, Kiniksa, Amgen, Otsuka, Cullinan, Quell, and OneFour Bio; and honoraria from Servier, Novartis, and Otsuka. CDB reports consultancy fees from Roche, AbbVie, GSK, Quell, and Takeda; honoraria from Pfizer and Genentech; and founding shares in Mestag Therapeutics. PE reports consultancy fees from Anatptysbio, Boehringer Ingelheim, Galapagos, Gilead, Immunovant, and Eli Lilly; honoraria from Eli Lilly and Boehringer Ingelheim; and support from attending meetings or travel from Eli Lilly. KM reports grants from AstraZeneca, Serac Healthcare, Deepcure, and Alfa Sigma; consultancy fees from AbbVie, ALLIn Bio, AstraZeneca, Galapagos, Engitix, Deepcure, Eli Lilly, Ventus Therapeutics, UCB, Zura Bio, and Alfa Sigma; honoraria from UCB, Alfa Sigma, and AbbVie; and support for attending meetings or travel from UCB and Alfa Sigma. PH reports honoraria from Novartis and UCB and support for attending meetings or travel from Novartis and UCB. MHB reports grants from Galapagos; consultancy fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Calluna Therapeutics, Elvara, Galapagos, Gilead, and Pfizer; honoraria from AbbVie, Boehringer Ingelheim, CESAS Medical, Medistream, Novo Nordisk, and Pfizer; and support for attending meetings or travel from Boehringer Ingelheim and UCB. REMT is named as inventor on a patent on the use of variable domain glycans on autoantibodies. All other authors declare that they have no other competing interests relating to this study.

Data sharing

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

Acknowledgments

The authors gratefully acknowledge funding from Bristol Myers Squibb, the invaluable contributions of the Trials Steering Committee (Chair: Deborah Symmons) and the Independent Data Monitoring Committee (Chair: Matt Sydes). We thank Mariam Al-Laith and Darshene Shivapatham, who were involved in the initial phase of study set up, members of the RTCure EU IMI consortium, and the National Rheumatoid Arthritis Society, who contributed valuable insight into the design of rheumatoid arthritis prevention studies through patient focus groups. The study also benefitted from infrastructure support at the National Institute for Health and Care Research (NIHR) Biomedical Research Centres and Clinical Research Facilities hosted by Guy's and St Thomas' NHS Foundation Trust and King's College London, University Hospitals Birmingham NHS Foundation Trust, NIHR Newcastle Biomedical Research Centre and Clinical Research Facility, University of Leeds and NIHR Leeds Biomedical Research Centre and NIHR University College London Hospital Biomedical Research Centre in London.

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