Evaluation of BMS-986142, a reversible Bruton's tyrosine kinase inhibitor, for the treatment of rheumatoid arthritis: a phase 2, randomised, double-blind, dose-ranging, placebo-controlled, adaptive design study

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Summary

Background Bruton's tyrosine kinase (BTK) is a promising biological target for rheumatoid arthritis treatment. This study examined safety, efficacy, and pharmacokinetics of BMS-986142, an oral, reversible BTK inhibitor. The aim was to compare the efficacy of BMS-986142 with placebo on a background of methotrexate in patients with moderate-to-severe rheumatoid arthritis and inadequate response to methotrexate.

Methods This phase 2, randomised, double-blind, dose-ranging, placebo-controlled, adaptive design study was conducted across 14 countries and 79 clinical sites. We recruited people aged 18 years or older with a documented diagnosis of rheumatoid arthritis at least 16 weeks before screening with an inadequate response to methotrexate with or without inadequate response to up to two tumour necrosis factor inhibitors. Participants were randomly assigned (1:1:1:1) to oral BMS-986142 (100 mg, 200 mg, or 350 mg) or placebo once daily for 12 weeks. Randomisation was done using an interactive voice response system and stratified by prior treatment status and geographical region. All participants, care providers, investigators, and outcome assessors were masked to treatment allocation. Co-primary endpoints were 20% and 70% improvement in American College of Rheumatology criteria (ACR20 and ACR70) at week 12. Primary endpoints were assessed in the efficacy analysis population (all randomised patients who received at least one dose of the study drug and did not discontinue the study). Safety endpoints were analysed in the as-treated analysis population, which included all patients who received at least one dose of the study drug (patients were grouped according to the treatment they actually received *vs* the treatment to which they were randomised). This trial was registered with ClinicalTrials.gov, number NCT02638948.

Findings Between Feb 24, 2016 and May 3, 2018, 248 patients were randomised (73 in the BMS-986142 100 mg group, 73 in the 200 mg group, 26 in the 350 mg group, and 75 in the placebo group; one post-randomisation exclusion); mean age was 56·7 years (SD 12·7); 214 (87%) of 247 were women, 33 (13%) were men, and 188 (76%) were White. Pre-specified interim analysis resulted in discontinuation of the 350 mg BMS-986142 dose due to elevated liver enzymes and absence of benefit versus placebo. Co-primary endpoints were not met. Response rates for ACR20 (placebo: 23 [31%] of 75; 100 mg: 26 [36%] of 73; 200 mg: 31 [42%] of 73) and ACR70 (placebo: three [4%] of 75; 100 mg: three [4%] of 73; 200 mg: seven [10%] of 73) were not significantly different to placebo; estimate of difference versus placebo for ACR20 was 4·9 (95% CI –10·2 to 20·1; p=0·52) for 100 mg and 11·8 (–3·6 to 27·2; p=0·14) for 200 mg, and for ACR70 the estimate of difference was 0·1 (–16·0 to 16·5; nominal p=1·00) for 100 mg and 5·6 (–10·5 to 21·9; nominal p=0·21) for 200 mg. Six patients experienced serious adverse events (four in the placebo group [mouth ulceration, open globe injury, rheumatoid arthritis flare, and endometrial adenocarcinoma] and two in the BMS-986142 100 mg group [angina pectoris and intestinal obstruction]); there were no deaths.

Interpretation Further investigation of BMS-986142 in people with rheumatoid arthritis is not warranted. An absence of clinical benefit in this study, together with other study results, highlights the need for additional research on the extent of BTK inhibition, treatment duration, and adequacy of drug distribution to inflammation sites, to understand the potential utility of BTK inhibition as a therapeutic strategy for rheumatoid arthritis.

Funding Bristol Myers Squibb.

Lancet Rheumatol 2023; 5: e263–73

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Introduction

Rheumatoid arthritis is a chronic, inflammatory, autoimmune disease affecting 0·5–1·0% of the global population.[1] As rheumatoid arthritis progresses, people experience many disease-related symptoms, including pain and joint stiffness, that coalesce and ultimately

Research in context

Evidence before this study

We searched PubMed using the following search terms: ("rheumatoid arthritis") AND ("Bruton's tyrosine kinase" OR "BTK") AND ("Randomized controlled trial" OR "Clinical trial" OR "RCT"), with no date or language restrictions applied. The evidence available before this study commenced was limited to two identified studies, neither of which were done in people with rheumatoid arthritis. Therefore, we also examined the full body of evidence before the writing of this Article in June 2022. From the 12 identified studies, only two published trials explored reversible or irreversible Bruton's tyrosine kinase (BTK) inhibitors in patients with rheumatoid arthritis. One trial was discontinued following an interim analysis, whereas the other (a proof-of-concept study) provided evidence for targeting BTK in patients with rheumatoid arthritis. BTK, a member of the Tec family of non-receptor tyrosine kinases, plays a pivotal part in the immune response and is a key mediator of the B-cell receptor and Fc-receptor signalling pathways central to the pathophysiology of autoantibody-mediated diseases such as rheumatoid arthritis. Although the existing clinical data investigating BTK inhibitors in people with rheumatoid arthritis are not as favourable as were preclinical results, the potential implications for achieving optimal BTK inhibition, combined with previous trial data, encourage further investigation. Further study will provide a better understanding of the role of underlying factors contributing to efficacy achievement (eg, the degree of inhibition needed for optimal efficacy and patient characteristics) that will help inform future development of BTK inhibitor therapies for the treatment of rheumatoid arthritis.

Added value of this study

This study examined the efficacy, safety, and pharmacokinetics of BMS-986142 (a reversible BTK inhibitor) in patients with rheumatoid arthritis. The co-primary endpoints (proportion of patients achieving 20% and 70% improvement according to American College of Rheumatology criteria) at week 12 were not met. The highest active dose (350 mg) was removed at interim analysis due to a risk–benefit assessment, whereas the 100 mg and 200 mg active treatment doses were well tolerated. In joint MRI outcomes, assessed using the Outcome Measures in Rheumatology Clinical Trials rheumatoid arthritis MRI score method, treatment with 200 mg BMS-986142 showed a significant mean difference in synovitis change compared with placebo at week 12. To our knowledge, this study is the first examination of BTK inhibitors on MRI outcomes. Expression of C-X-C motif chemokine ligand 13, an emerging prognostic biomarker, correlated with disease activity indices and showed a dose-dependent, moderate decrease over 12 weeks. Considering the variable and inconsistent pharmacokinetics of BMS-986142, it is possible that this compound might not have achieved sufficient BTK inhibition based on its pharmacokinetic and pharmacodynamic profile.

Implications of all the available evidence

There is still a need in routine clinical management of rheumatoid arthritis for therapeutics with novel mechanisms of action. The mechanism of action of BTK inhibition appears relevant in rheumatoid arthritis, but sufficient inhibition of the pathway might not have been achieved with this reversible BTK inhibitor. Our results, combined with those from other studies, highlight the need for additional research to understand the role of (1) the extent of BTK inhibition via reversible and irreversible BTK inhibitors; (2) the effect of a longer duration of treatment than already studied; and (3) the distribution of the drug to sites of inflammation, in the utility of BTK inhibition as a potential therapeutic strategy for people with rheumatoid arthritis.

diminish patients' quality of life.[2,3] Although a number of effective rheumatoid arthritis therapies are available with different mechanisms of action, not all patients respond adequately to these and there remains a need for additional therapies with novel mechanisms of action that can provide both alternatives to, and synergy with, current therapeutic approaches.

Bruton's tyrosine kinase (BTK) is a promising biological target for rheumatoid arthritis treatment.[4] BTK, expressed by several immune cell types, is a member of the Tec family of non-receptor tyrosine kinases.[5] BTK plays a major role in the immune response and is a key mediator of the B-cell receptor and Fc-receptor signalling pathways central to the pathophysiology of autoantibody-mediated diseases such as rheumatoid arthritis.[6,7] Despite having shown efficacy in murine models of systemic autoimmune disease,[7–9] few published data exist exploring reversible or irreversible BTK inhibitors in the clinical setting in patients with rheumatoid arthritis.[10–12] A better understanding of the role of factors contributing to efficacy, such as the degree of BTK inhibition and identification of biomarkers that predict treatment response, will help to inform the development of BTK inhibitors for rheumatoid arthritis and personalised medicine efforts. To our knowledge, no studies have examined MRI joint outcomes for BTK inhibitors. MRI outcomes provide a sensitive, tissue-level assessment, offering further insight into disease status, progression, and treatment response.

BMS-986142, an oral, reversible BTK inhibitor, has shown promising efficacy in animal models of rheumatoid arthritis by reducing joint inflammation and destruction when compared with standard-of-care treatment.[8] In a combined single-ascending dose (5–900 mg) and multiple-ascending dose (25–350 mg; once daily for 14 days) study among healthy participants, BMS-986142 was well tolerated across doses, with pharmacokinetic and pharmacodynamic profiles

supporting once-daily dosing; there was no clinically significant drug–drug interaction when co-administered with methotrexate.[13] The primary study objective was to compare the efficacy of BMS-986142 with placebo on a background of methotrexate in patients with moderate-to-severe rheumatoid arthritis and inadequate response to methotrexate, with or without inadequate response to up to two tumour necrosis factor (TNF) inhibitors. Additional objectives included comparisons of clinical response biomarkers (ie, MRI), safety and tolerability, and evaluation of pharmacokinetics and BTK pathway biomarkers of interest.

Methods

Study design

This was a phase 2, randomised, multicentre, double-blind, dose-ranging, placebo-controlled, adaptive design study (appendix pp 2–4) to evaluate the efficacy, safety, and pharmacokinetics of BMS-986142 in patients with moderate-to-severe rheumatoid arthritis with inadequate response to methotrexate, with or without inadequate response to TNF inhibitors (appendix p 5). The study was conducted from Feb 24, 2016 to May 3, 2018, at clinical sites in the following countries: Argentina, Brazil, Canada, France, Italy, Japan, South Korea, Mexico, Poland, Russia, South Africa, Spain, Taiwan, and the USA.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol and patients' informed consent received institutional review board and independent ethics committee approval before initiation of the study.

Patients

The patient population comprised men and women aged 18 years or older with a documented diagnosis of adult-onset rheumatoid arthritis at least 16 weeks before screening, as defined by standard criteria (American College of Rheumatology [ACR] and European Alliance of Associations for Rheumatology [2010]).[14] To be eligible, participants had to have an ACR global function status class of 1–3; an inadequate response to methotrexate, as determined by the investigator; been receiving methotrexate for at least 3 months at a weekly dose of 15 mg or higher (or 10 mg or higher methotrexate at screening, if toxicity or intolerance was experienced); been on a stable methotrexate dose during the 4 weeks before randomisation; not achieved an adequate response to up to two TNF inhibitors, as determined by the investigator; at least six swollen and at least six tender joints on a 66/68 joint count; evidence of swelling in one or more joints of the hand or wrist; and a high-sensitivity C-reactive protein (CRP) concentration of 0·8 mg/dL or higher or an erythrocyte sedimentation rate (ESR) of 28 mm/hour or higher. The objective for the patient population was to include at least 70% of patients with inadequate response to methotrexate and less than 30% with inadequate response to methotrexate and inadequate response to up to two TNF inhibitors. Main exclusion criteria were documented juvenile rheumatoid arthritis or Felty's syndrome; reported use of biologic disease-modifying antirheumatic drugs other than TNF inhibitors; immunomodulatory treatment other than methotrexate at study outset; intra-muscular or intra-articular glucocorticoid treatment up to 4 weeks before randomisation; risk of tuberculosis; reported bacterial infection (≤60 days previously) unless treated and resolved, or any chronic or history of recurrent bacterial infection; or history of systemic fungal infections. Information on sex was collected using case report forms; available options were male or female. All patients gave written informed consent. The protocol is available via ClinicalTrials.gov (https://www.clinicaltrials.gov/ProvidedDocs/48/NCT02638948/Prot_000.pdf).

See Online for appendix

Randomisation and masking

After completing all screening evaluations, eligible patients were randomly assigned (1:1:1:1) to one of four treatment groups: BMS-986142 100 mg, 200 mg, 350 mg, or placebo; all treatment was administered orally once daily. To randomise a participant, a phone call was placed into the interactive voice response system to obtain a randomised treatment assignment. Randomisation was assigned by the order in which patients qualified for treatment and was stratified by prior treatment status (ie, inadequate response to methotrexate and inadequate response to TNF inhibitors) and geographical region. Following randomisation, masked study treatment (or matched placebo in the form of tablets with identical appearance) was dispensed according to the treatment assignment. All participants, care providers, investigators, and outcome assessors were masked to treatment allocation.

Procedures

The study included a screening period (≤28 days); a 12-week, double-blind treatment period; and a 30-day follow-up period. Doses of methotrexate, non-steroidal anti-inflammatory drugs, and oral prednisone (or equivalent) were to remain stable; intra-articular and intra-muscular corticosteroid injections were not permitted during the double-blind treatment period. Pre-specified relevant protocol deviations that could affect the primary endpoint were identified before database lock with unmasking of treatment assignment.

Outcomes

The co-primary endpoints of the study were the proportion of patients who achieved 20% and 70% improvement in ACR criteria (ACR20 and ACR70) at week 12, which were assessed in a staged manner. The components of the ACR responses were collected at the individual sites and then ACR response rates were analysed centrally (Bristol Myers Squibb; Lawrenceville, NJ, USA).

Key secondary clinical endpoints included the proportion of patients who achieved the following: 50% improvement in ACR criteria (ACR50) at week 12, Disease Activity Score in 28 joints (DAS28)-CRP less than 2·6, DAS28-ESR less than 2·6, Clinical Disease Activity Index (CDAI) remission (score ≤2·8), Simplified Disease Activity Index (SDAI) remission (score ≤3·3), and Boolean remission. MRI assessments of synovitis, osteitis, bone erosion, and joint space narrowing were done according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) rheumatoid arthritis MRI score (RAMRIS) definitions and scoring methods.[15] Initial assessments of the metacarpophalangeal joints were collected during screening on the more clinically inflamed hand or wrist with the greater swollen joint count, and were repeated at weeks 4 and 12 on the same hand or wrist. Discontinuations, and incidence and severity of adverse events, serious adverse events, and pre-established events of special interest were examined by system organ class and preferred term. Plasma pharmacokinetic analysis of BMS-986142 trough concentration was done at weeks 4, 8, and 12 (days 29, 57, and 85, respectively). Exploratory endpoints included measurement of plasma concentrations of the B-cell-specific chemokine, C-X-C motif chemokine 13 (CXCL13; by ELISA; Myriad RBM, Austin, TX, USA), and RNA expression of target plasma and plasmablast gene signatures by quantitative PCR. Target genes selected to evaluate the effects of BTK-mediated B-cell development included joining chain of multimeric IgA and IgM (*JCHAIN*), TNF receptor superfamily member 17 (*TNFRSF17*), syndecan 1 (*SDC1*), immunoglobulin heavy constant alpha 1 (*IGHA1*), and marginal zone B and B1 cell-specific protein (*MZB1*). Prespecified study endpoints are listed in the appendix (pp 17–18). In addition, exploratory post-hoc subgroup analyses were performed based on anti-citrullinated protein antibody (ACPA) status.

Statistical analysis

Interim analysis was done on all available data for changes from baseline in DAS28 up to week 12 using a Bayesian predictive approach.[16] The Bayesian and dose exposure–response analyses determined whether new doses were needed to fully characterise the dose–efficacy relationship. The pre-specified efficacy endpoint (DAS28) was assessed with exposure endpoints to guide the selection of new dose levels in different scenarios (appendix pp 2–4).

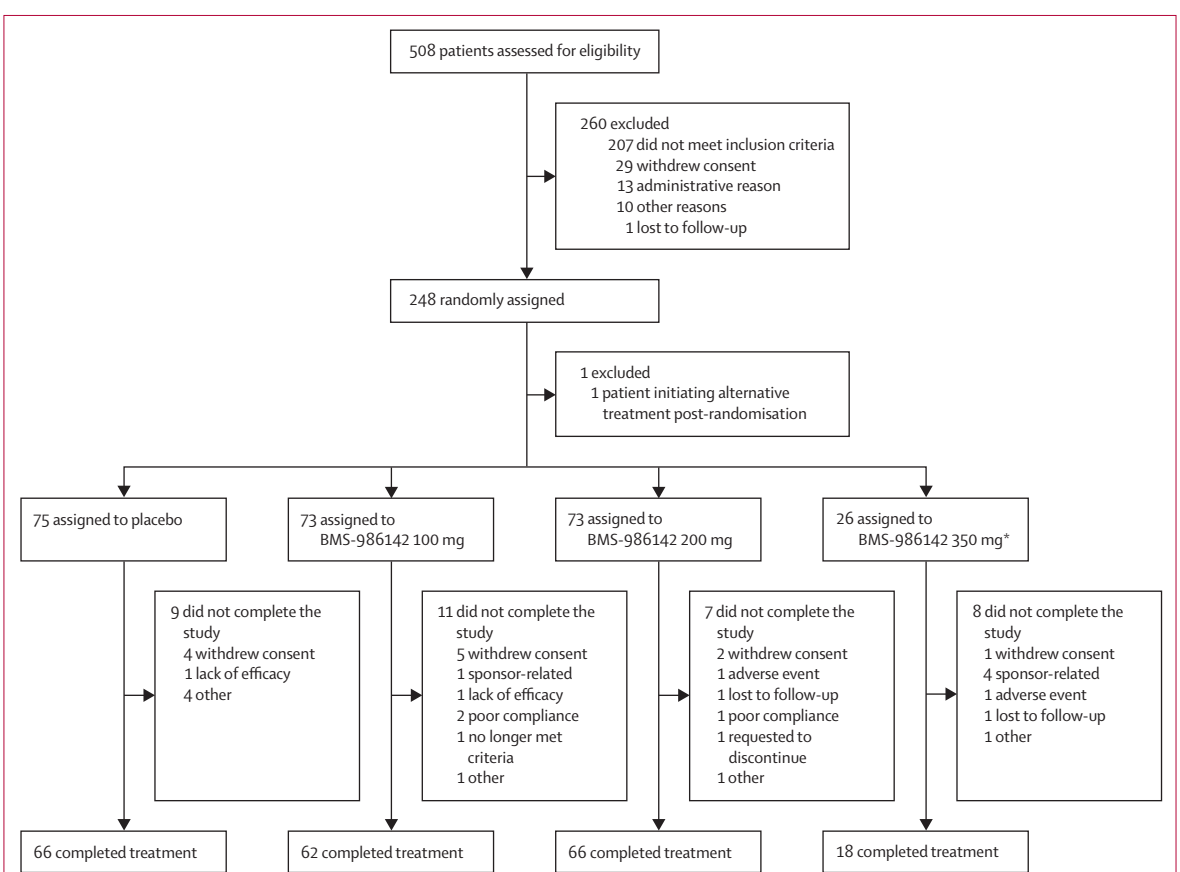

Figure 1: **Trial profile**
*Group discontinued on the basis of the interim analysis.

Interim analysis results were reviewed by an unmasked team not involved in the study who then provided recommendations with regard to adaptive design decisions to the masked study team. On the basis of the totality of safety and efficacy evaluations, ineffective treatment doses were to be stopped at week 12; unsafe doses were to be discontinued immediately.

Primary analyses were performed across active treatment and placebo groups. Secondary, exploratory, and post-hoc statistical analyses are described in the appendix (pp 2–4). Administration of BMS-986142 to around 82 patients in each treatment group provided around 80% power in detecting a treatment difference of 14% compared with placebo for the co-primary endpoint of ACR70 at week 12 (type I error rate [α]=0·05 [two-sided]), assuming a placebo response rate of 2·5%.

For the co-primary endpoints, χ^2 tests compared response rates at week 12 between each of the active treatment groups and the placebo group, with p values provided for each comparison. Within each treatment group, statistical testing was performed for ACR20 first; if testing revealed a significant difference, testing was performed for ACR70; alternatively, if the testing did not reveal a significant difference, statistical testing was stopped for this treatment group. Primary endpoints were assessed in the efficacy analysis population, a subset of the modified intention-to-treat analysis population (all randomised participants who received at least one dose of study drug; participants were grouped according to the treatment to which they were allocated at the start of the study) that excluded participants who were randomised to a treatment group and discontinued on the basis of the interim analysis.

The number and proportion of patients who experienced at least one adverse event were summarised by treatment groups for the most common adverse events (≥5% of patients in any treatment group; exposure-adjusted adverse events). Safety endpoints were analysed in the as-treated analysis population, which included all participants who received at least one dose of study drug (participants were grouped according to the treatment they actually received *vs* the treatment to which they were randomised). Summary statistics for trough concentrations of BMS-986142 (ie, geometric mean and percent coefficient of variation [%CV]) were provided for the pharmacokinetic analysis population (all patients who received BMS-986142 and had concentration–time data available) by dose and study day (days 29, 57, and 85).

Statistical analysis was done in SAS (version 9.03). A data monitoring committee reviewed the data. This trial was registered with ClinicalTrials.gov, number NCT02638948.

Role of the funding source

The funder of the study had a role in the study design, data collection, data analysis, data interpretation, writing of the report, and in the decision to submit for publication.

Results

Across 14 countries and 79 clinical sites, 508 patients were assessed for eligibility between Feb 24, 2016 and

	Placebo group (n=75)	100 mg group (n=73)	200 mg group (n=73)	350 mg group (n=26)
Age, years	58·6 (11·6)	57·6 (13·0)	55·2 (13·1)	52·9 (13·2)
Sex*				
Female	64 (85%)	67 (92%)	62 (85%)	21 (81%)
Male	11 (15%)	6 (8%)	11 (15%)	5 (19%)
Race				
White	52 (69%)	54 (74%)	58 (79%)	24 (92%)
Black or African American	6 (8%)	9 (12%)	5 (7%)	1 (4%)
Asian	14 (19%)	8 (11%)	8 (11%)	1 (4%)
Other	3 (4%)	2 (3%)	2 (3%)	0
Prior treatment status				
Methotrexate inadequate response	60 (80%)	60 (82%)	59 (81%)	21 (81%)
Anti-TNF inadequate response†	15 (20%)	13 (18%)	14 (19%)	5 (19%)
Duration of rheumatoid arthritis, years	9·6 (8·7)	9·4 (11·5)	7·7 (7·8)	7·3 (9·4)
ACPA-positive	54 (72%)	44 (60%)	43 (59%)	18 (69%)
Rheumatoid factor-positive	46 (61%)	44 (60%)	44 (60%)	17 (65%)
DAS28-CRP	5·6 (1·0)	5·6 (1·0)	5·6 (0·9)	5·7 (0·9)
DAS28-ESR	6·4 (1·0)	6·3 (1·0)	6·4 (0·9)	6·4 (0·9)
CDAI	39·4 (12·9)	38·5 (14·0)	38·5 (12·0)	38·0 (11·0)
SDAI	40·7 (13·4)	40·0 (14·1)	39·5 (12·5)	40·3 (12·4)
Tender joint count	23·9 (14·7)	22·7 (13·4)	23·9 (13·0)	22·0 (15·2)
Swollen joint count	16·1 (11·8)	16·1 (9·7)	13·6 (7·7)	15·0 (10·0)
Pain (VAS), mm	63·2 (22·9)	65·8 (24·6)	66·6 (22·4)	67·8 (23·0)
HAQ	1·6 (0·6)	1·7 (0·6)	1·5 (0·7)	1·5 (0·5)
Patient Global Assessment	64·4 (22·7)	61·3 (24·3)	66·9 (21·8)	62·6 (30·0)
Physician Global Assessment	65·5 (14·9)	66·7 (20·6)	65·4 (20·4)	57·8 (18·1)
High-sensitivity CRP, mg/L	13·2 (24·3)	15·7 (19·7)	10·5 (12·5)	22·1 (30·8)
ESR, mm/hour	42·6 (22·3)	39·0 (19·6)	36·4 (17·6)	45·5 (24·0)
Prednisone daily, mg	4·7 (2·6)	5·8 (3·0)	4·5 (2·3)	5·4 (3·2)
Patients on corticosteroids	30 (40%)	27 (37%)	22 (30%)	15 (58%)
Methotrexate weekly dose, mg	16·7 (9·9)	19·0 (12·7)	15·9 (3·6)	16·3 (3·0)
RAMRIS parameters				
Synovitis	7·6 (4·3; n=73)	8·4 (4·8; n=71)	7·3 (4·3; n=73)	8·1 (5·0; n=26)
Osteitis	8·3 (8·4; n=68)	8·2 (7·3; n=66)	7·3 (9·0; n=71)	8·2 (8·5; n=23)
Bone erosion	17·2 (30·6; n=73)	11·8 (15·5; n=72)	9·4 (16·4; n=73)	14·7 (26·3; n=26)
Joint space narrowing	21·4 (17·8; n=72)	22·0 (15·9; n=71)	17·7 (15·0; n=72)	23·8 (17·7; n=26)

Data are presented as mean (SD) or n (%), unless otherwise stated. All doses for the active treatment groups were administered once daily. ACPA=anti-citrullinated protein antibody. CDAI=Clinical Disease Activity Index. CRP=C-reactive protein. DAS28=Disease Activity Score in 28 joints. ESR=erythrocyte sedimentation rate. HAQ=Health Assessment Questionnaire. RAMRIS=Rheumatoid Arthritis Magnetic Resonance Imaging Score. SDAI=Simplified Disease Activity Index. TNF=tumour necrosis factor. VAS=visual analogue scale. *Options given in the case report form were male or female. †In addition to methotrexate inadequate response.

Table 1: **Baseline demographics and disease characteristics**

May 3, 2018. Of these, 248 patients were randomised in the study and 260 patients were excluded (figure 1). Following randomisation, one participant was excluded (initiated treatment with a medication causing exclusion), resulting in 75 participants randomly assigned to the placebo group, 73 participants to the 100 mg group, 73 participants to the 200 mg group, and 26 participants to the 350 mg group. A summary of relevant protocol deviations is provided (appendix p 19). For the overall population, participants had a mean age of 56·7 years (SD 12·7); 214 (87%) of 247 participants were women, 33 (13%) were men, and 188 (76%) were White. Across treatment groups, baseline demographic and disease characteristics were generally well balanced (table 1). Due to a small number of patients with inadequate response to TNF inhibitors (n=47), the exploratory subgroup analysis included only patients with inadequate response to methotrexate (n=200).

From the initial 247 patients enrolled, 212 (86%) completed the study (placebo group: 66 [88%] of 75; 100 mg group: 62 [85%] of 73; 200 mg group: 66 [90%] of 73; and 350 mg group: 18 [69%] of 26; figure 1). Following the pre-specified interim analysis (figure 1), participants randomly allocated to the 350 mg group discontinued treatment; the risk–benefit ratio assessment noted elevation of aminotransferases and an absence of benefit compared with placebo. Results for co-primary, key secondary, and exploratory endpoints from the 350 mg group are presented in the appendix (p 20).

The co-primary endpoints of ACR20 and ACR70 at week 12 were not met. ACR20 and ACR70 response rates in participants receiving BMS-986142 (100 mg or 200 mg) were not significantly different to placebo (table 2; appendix p 6). As the co-primary endpoints were not met, secondary and exploratory endpoints should be considered as hypothesis-generating only.

At week 12, ACR50 response rates were similar across treatment groups (table 2; appendix p 6). Mean changes from baseline to week 12 in DAS28-CRP and DAS28-ESR were similar across groups (appendix p 7). There were no notable differences between treatment groups in response as assessed by components of DAS28-CRP (appendix p 8). Across all treatment groups, at week 12, few patients achieved a DAS28-CRP of less than 2·6, CDAI remission, SDAI remission, or Boolean remission (table 2).

ACR20, ACR50, and ACR70 responses at week 12 by sex are shown in the appendix (p 21). As most participants in the study were female (87%), responses among women were similar to the overall population; sample sizes for men per treatment group were too small to draw any conclusions.

Baseline MRI scores were similar across treatment groups (table 1). Overall, changes from baseline in RAMRIS parameters at week 12 were variable across active treatment and placebo groups, with the 200 mg dose providing the greatest effect across outcomes (figure 2; appendix p 23). In the placebo group at week 12, synovitis showed significant progression from

	Placebo group (n=75)	100 mg group (n=73)	Difference *vs* placebo	200 mg group (n=73)	Difference *vs* placebo
Co-primary endpoints					
ACR20					
Responders, n (%; 95% CI)	23 (31%; 20 to 41)	26 (36%; 25 to 47)	4·9 (–10·2 to 20·1; p=0·52)	31 (42%; 31 to 54)	11·8 (–3·6 to 27·2; p=0·14)
Imputed responses*,n (%)	10 (13%)	10 (14%)	NA	5 (7%)	NA
ACR70					
Responders, n (%; 95% CI)	3 (4%; 1 to 11)	3 (4%; 1 to 12)	0·1 (–16·0 to 16·5; nominal p=1·00)	7 (10%; 3 to 16)	5·6 (–10·5 to 21·9; nominal p=0·21)
Imputed responses*, n (%)	9 (12%)	10 (14%)	NA	5 (7%)	NA
Secondary endpoints, n (%; 95% CI)					
ACR50 responders	7 (9%; 3 to 16)	10 (14%; 6 to 22)	4·4 (–5·9 to 14·6)	12 (16%; 8 to 25)	7·1 (–3·6 to 17·9)
DAS28-CRP <2·6	5 (7%; 1 to 12)	7 (10%; 3 to 16)	2·9 (–5·9 to 11·7)	8 (11%; 4 to 18)	4·3 (–4·8 to 13·4)
DAS28-ESR <2·6	0 (0 to 5)	5 (7%; 1 to 13)	6·8 (–9·4 to 23·1)	1 (1%; 0 to 7)	1·4 (–14·9 to 17·7)
CDAI ≤2·8	0 (0 to 5)	5 (7%; 1 to 13)	6·8 (–9·4 to 23·1)	5 (7%; 1 to 13)	6·8 (–9·4 to 23·1)
SDAI ≤3·3	0 (0 to 5)	5 (7%; 1 to 13)	6·8 (–9·4 to 23·1)	5 (7%; 1 to 13)	6·8 (–9·4 to 23·1)
Boolean remission†	1 (1%; 0 to 7)	3 (4%; 1 to 12)	2·8 (–13·5 to 19·1)	3 (4%; 1 to 12)	2·8 (–13·5 to 19·1)

All doses for the active treatment groups were administered once daily. The 350 mg dose group was discontinued following interim analyses and is not included in this table. For the CI of the response rate within each treatment group, the normal approximation was used if the number of responders (numerator) was five or higher, and the total number of patients in the analysis (denominator) was at least five more, otherwise the exact method was used. For the CI of the difference between groups, normal approximation was used if, in both groups, the number of responders (numerator) was five or higher, and the total number of patients in the analysis (denominator) was at least five more, otherwise the exact method was used. ACR20/50/70=20%/50%/70% improvement in American College of Rheumatology criteria. CDAI=Clinical Disease Activity Index. CRP=C-reactive protein. DAS28=Disease Activity Score in 28 joints. ESR=erythrocyte sedimentation rate. NA=not applicable. SDAI=Simplified Disease Activity Index. *Missing data for binary outcomes were imputed as non-responders. †Patients satisfying all of the following conditions were defined as having Boolean remission: tender joint count 28 ≤1; swollen joint count 28 ≤1; clinician's global assessment ≤1; and CRP ≤1 mg/dL.

Table 2: **Summary of co-primary and key secondary clinical endpoint results at week 12**

baseline (0·54 [95% CI 0·04 to 1·04]; nominal p=0·033). The 200 mg group showed a significant mean difference versus placebo in synovitis change from baseline at week 12 (–0·99 [95% CI –1·67 to –0·31]; nominal p=0·005; figure 2; appendix p 23). In the 100 mg group, bone erosion and joint space narrowing showed significant increases from baseline at week 12 (figure 2).

Adverse event frequency and intensity were similar across groups, with the exception of the 350 mg group, in which a greater proportion of participants experienced adverse events than in the other groups (table 3). Overall, the 100 mg and 200 mg doses of BMS-986142 were well tolerated and had an acceptable safety profile. Six patients experienced serious adverse events (four in the placebo group [mouth ulceration, open globe injury, rheumatoid arthritis flare, and endometrial adenocarcinoma] and two in the BMS-986142 100 mg group [angina pectoris and intestinal obstruction]). Adverse events leading to discontinuation occurred in 11 (6%) of 172 participants (10 in the active treatment groups and 1 in the placebo group; table 3). No deaths were reported during the study.

At all three timepoints assessed (days 29, 57, and 85), geometric mean trough concentrations of BMS-986142 increased with dose. Over time, trough concentrations decreased in the 100 mg group (day 29: 47·9 ng/mL [n=60]; day 57: 41·2 ng/mL [n=54]; day 85: 28·4 ng/mL [n=55]) and 200 mg group (day 29: 111·8 ng/mL [n=61]; day 57: 92·2 ng/mL [n=60]; day 85: 75·6 ng/mL [n=52]). There was high interpatient variability (%CV) across timepoints and dose groups (100 mg group: 95–123%; 200 mg group: 102–155%; 350 mg group: 83–133%).

Biomarker data include the 350 mg group (appendix pp 9–12, 14–15, and 22) to provide information on the dose-dependent relationship between BMS-986142 and the selected biomarkers; this is not described in the text because this dose was discontinued following the pre-specified interim analysis. Biomarker

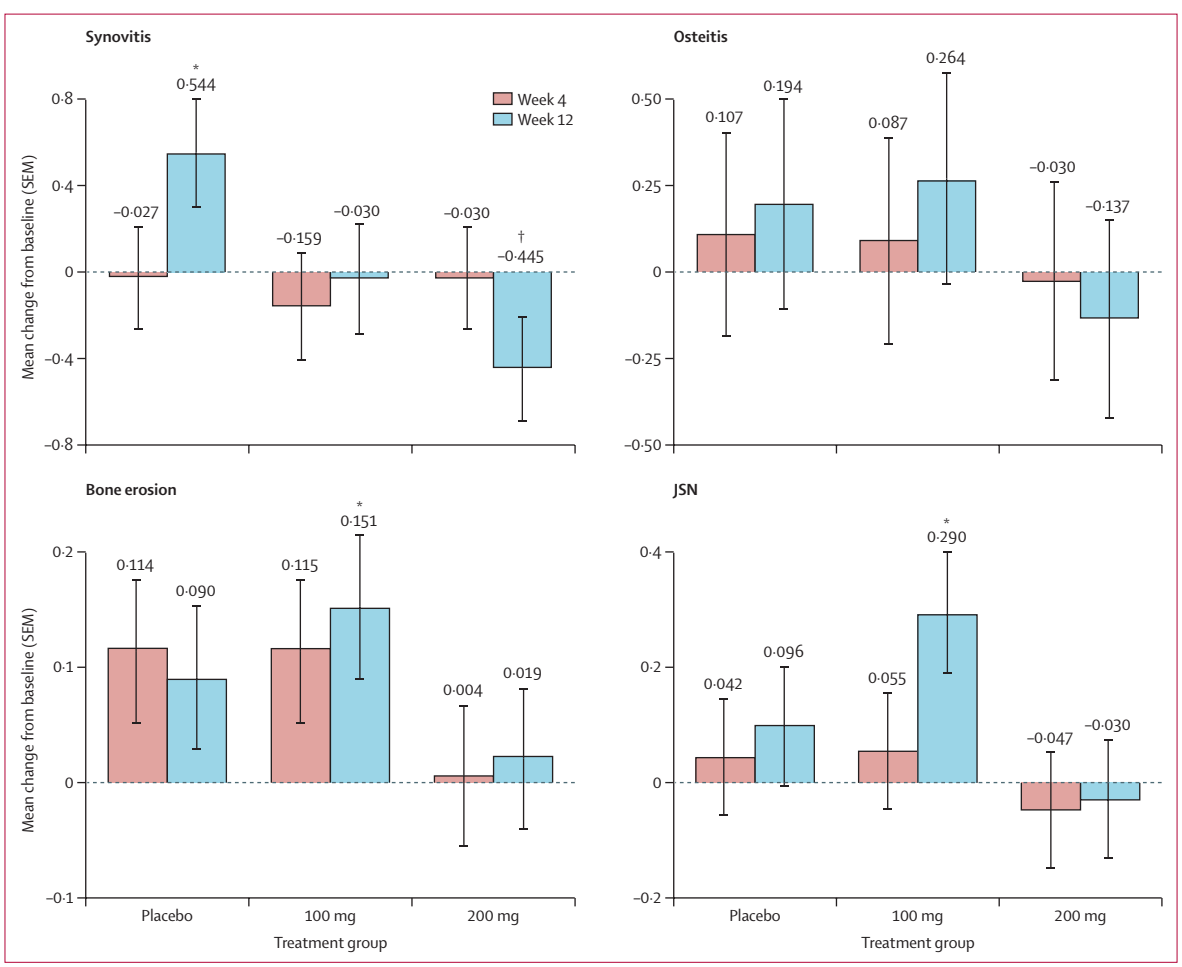

Figure 2: **Change from baseline in RAMRIS parameters at weeks 4 and 12 by treatment group**
350 mg dose group was discontinued following interim analyses and is not included in these figures. Model-adjusted marginal mean changes from baseline are estimated from linear mixed-effects models including treatment, week, treatment–week interaction, baseline value, and baseline steroid use with a random intercept for patient. JSN=joint space narrowing. RAMRIS=Rheumatoid Arthritis Magnetic Resonance Imaging Score. SEM=standard error of the mean. *Significant change from baseline (unadjusted p value). †Significant difference compared with placebo (unadjusted p value).

	Placebo group (n=75)	100 mg group (n=73)	200 mg group (n=73)	350 mg group* (n=26)
Deaths	0	0	0	0
Serious adverse events	4 (5%)	2 (3%)	0	0
Treatment-related serious adverse events	0	0	0	0
Discontinued due to serious adverse events	0	1 (1%)	0	0
Adverse events	36 (48%)	39 (53%)	39 (53%)	19 (73%)
Treatment-related adverse events	14 (19%)	13 (18%)	21 (29%)	12 (46%)
Discontinued due to adverse events	1 (1%)	3 (4%)	4 (5%)	3 (12%)
System organ class preferred term†				
Infections and infestations	13 (17%)	18 (25%)	15 (21%)	8 (31%)
Urinary tract infections	1 (1%)	5 (7%)	5 (7%)	5 (19%)
Nasopharyngitis	2 (3%)	4 (5%)	3 (4%)	0
Metabolism and nutrition disorders	3 (4%)	5 (7%)	9 (12%)	7 (27%)
Dyslipidaemia	2 (3%)	1 (1%)	3 (4%)	6 (23%)
Liver enzyme concentrations	5 (7%)	2 (3%)	6 (8%)	8 (31%)
Increased ALT	3 (4%)	0	1 (1%)	5 (19%)
Increased ALP	0	0	0	4 (15%)
Increased AST	2 (3%)	0	1 (1%)	2 (8%)
Nervous system disorders	5 (7%)	6 (8%)	6 (8%)	2 (8%)
Headache	2 (3%)	2 (3%)	4 (5%)	2 (8%)
Blood and lymphatic system disorders	1 (1%)	1 (1%)	4 (5%)	2 (8%)
Anaemia	1 (1%)	1 (1%)	3 (4%)	2 (8%)

Data are presented as n (%). All safety presentations were based on the as-treated population. ALP=blood alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Patients randomly assigned to 350 mg BMS-986142 discontinued treatment following interim analyses at week 4 but then completed safety follow-up visits. †Most common adverse events during 12 weeks treatment and 30 days after the last dose in at least 5% of participants.

Table 3: **Adverse events during 12 weeks of treatment and 30 days after the last dose**

results at week 12 are described in the text and shown in the figures. Additional results are shown in the appendix (p 22).

Compared with participants treated with placebo, participants treated with BMS-986142 (both 100 mg and 200 mg) showed reductions in CXCL13 concentrations from baseline across all timepoints (appendix pp 9–10). At week 12, there was a significant difference in percent change from baseline between the 200 mg and placebo groups (nominal p=0·004), but not between the 100 mg and placebo groups (nominal p=0·18). Congruent with the mechanism of action of BMS-986142, expression of target plasma cell genes (*JCHAIN*, *SDC1*, *TNFRSF17*, *IGHA1*, and *MZB1*) decreased over time in both the 100 mg and 200 mg groups compared with placebo (appendix pp 9–12). For example, compared with placebo at week 12, significant differences for the active treatment groups were seen for *JCHAIN* (200 mg group, nominal p=0·003), *SDC1* (100 mg group, nominal p=0·047; 200 mg group, nominal p=0·003), *IGHA1* (200 mg group, nominal p=0·023), and *MZB1* (200 mg group, nominal p=0·031). No significant differences were observed between placebo and active treatment groups for *TNFRSF17*.

A significant but moderate correlation between changes in CXCL13 and CDAI was seen in the 200 mg group (ρ=0·41, nominal p=0·0015) but not in the 100 mg group (ρ=0·21, nominal p=0·13; appendix p 13). A weak correlation was observed for the placebo group (ρ=0·28, nominal p=0·031). Weak-to-moderate correlations were also noted between CXCL13 expression and synovitis in the active treatment groups (100 mg group: ρ=0·45, nominal p=0·0014; 200 mg group: ρ=0·24, nominal p=0·076; appendix p 13). The correlation was negligible for the placebo group (ρ=0·049, nominal p=0·72). Lastly, a significant correlation was observed between CXCL13 percent change and DAS28-CRP change for the 200 mg group (ρ=0·39, nominal p=0·0032) and weaker correlations for the 100 mg group (ρ=0·23, nominal p=0·086) and the placebo group (ρ=0·33, nominal p=0·011; appendix p 13).

Although variable, concentrations of IgA, IgG, and IgM generally showed dose-dependent reductions from baseline at week 12 (appendix pp 14–15).

Subgroup analyses of ACR20 response rates by ACPA positivity (appendix p 16) showed that, among ACPA-positive participants, rates were significantly greater in those receiving 200 mg (19 [56%] of 34; nominal p=0·040) than in those receiving placebo (14 [33%] of 43); the rate in ACPA-positive participants receiving 100 mg (12 [38%] of 32; nominal p=0·66) was not significantly higher than that in those receiving placebo. ACR20 responses in ACPA-negative participants randomly assigned to 100 mg (nine [36%] of 25; p=0·46) or 200 mg (seven [33%] of 21; p=0·58) were not significantly higher than that in ACPA-negative participants randomly assigned to placebo (four [25%] of 16).

Post-hoc analyses of synovitis in ACPA-positive participants receiving placebo showed a significant increase from baseline at week 12 (0·77 [95% CI 0·13 to 1·41]; nominal p=0·019; appendix p 16). Among ACPA-positive participants in the 100 mg group, there were marginal changes from baseline in synovitis, whereas the 200 mg group showed a significant decrease from baseline at week 12 (–0·76 [–1·46 to –0·07]; nominal p=0·032). There was a significant mean difference in change from baseline between ACPA-positive participants receiving 200 mg and placebo (–1·53 [–2·46 to –0·60]; nominal p=0·001). No significant changes from baseline or differences between active treatment groups and placebo were seen in ACPA-negative participants.

Discussion

The purpose of this study was to examine the efficacy, safety, and pharmacokinetics of BMS-986142 versus placebo on a background of methotrexate in patients with rheumatoid arthritis. Co-primary endpoints (ACR20 and ACR70 at week 12) were not achieved. The development of this compound in rheumatoid arthritis was discontinued based on the absence of clinical efficacy

shown in this study. For the purposes of hypothesis generation, results for other clinical and biomarker outcomes with BMS-986142 versus placebo collected in this study are reported, to provide insight towards improving future research of BTK inhibitors for the treatment of people with rheumatoid arthritis.

A pre-specified risk–benefit interim analysis led to the discontinuation of the 350 mg treatment group. Although exploratory analysis of changes in soluble biomarker data showed a dose-dependent effect, discontinuation precluded the ability to fully explore this dose level. Thus, one additional hypothesis for why BMS-986142 was not successful in achieving co-primary endpoints might have resulted from dose-limiting toxicity. As such, the observations on BMS-986142, and the variable results seen with other BTK inhibitors in rheumatoid arthritis,[10–12] might be partly explained by the extent of BTK inhibition each compound can safely achieve. Co-administration with methotrexate can also contribute to dose limitations. Other factors include the possibility that the duration of therapy required to see a treatment benefit is longer than what is possible (due to ethical and regulatory requirements) in early clinical studies of compounds in rheumatoid arthritis. Additionally, such results could be related to effects on tissue distribution and whether sufficient inhibition can be achieved at appropriate sites given any dose or duration limitations.

To date, few study data have been published on BTK inhibitors in people with rheumatoid arthritis. A 12-week study in patients positive for rheumatoid factor and ACPA who were randomly assigned to receive fenebrutinib (50 mg once daily, 150 mg once daily, or 200 mg twice daily), adalimumab (40 mg every other week), or placebo, showed that higher doses of fenebrutinib (150 mg once daily or 200 mg twice daily) showed significant improvements in ACR50 compared with placebo (28% [150 mg once daily] and 35% [200 mg twice daily] *vs* 15% [placebo]).[10] In a 4-week study, patients with active rheumatoid arthritis on background methotrexate therapy were randomly assigned to receive oral spebrutinib (375 mg once daily) or placebo.[11] Patients treated with spebrutinib did not show significantly greater ACR20 responses than those treated with placebo. Most recently, elsubrutinib (an irreversible BTK inhibitor) achieved more than 90% BTK engagement but failed to achieve significant improvements compared with placebo at 12 weeks.[12] Additional studies have examined alternative BTK inhibitors (eg, evobrutinib, tirabrutinib, and acalabrutinib) in people with rheumatoid arthritis, but have not been fully published.[17,18]

To our knowledge, this study is the first evaluation of BTK inhibition on joint MRI outcomes. The study used the validated OMERACT RAMRIS definition and scoring system,[15,19] assessing inflammation as well as structural damage. In small, early-phase trials that were not powered for radiographic endpoints, MRI measures of inflammation were useful exploratory endpoints as they predicted subsequent radiographic progression.[20–24] In general, baseline data were as expected; although observed changes were not significantly different between groups, the directionality of the changes was as expected. Of note, compared with placebo, the 200 mg group showed a nominally significant improvement in synovitis, although it should be acknowledged that this did not result in notable clinical benefit with BMS-986142 treatment for patients in this study. Structural damage parameters showed minimal and non-significant progression, with the least amount of progression evident in the 200 mg group. Short study duration might have contributed to this finding, as 12 weeks could have been too early to identify structural damage changes. In a post-hoc analysis, a large and nominally significant improvement in synovitis compared with placebo was seen for the subgroup of ACPA-positive participants in the 200 mg group. Similarly, this subgroup of ACPA-positive participants (receiving 200 mg) showed nominally significantly greater ACR20 responses than did ACPA-positive participants receiving placebo. Although the sample size was small, improved responses in this rheumatoid arthritis subgroup support previous observations that show that ACPA positivity is associated with improved outcome responses.[25,26] As such, people with ACPA-positive rheumatoid arthritis might represent a subgroup of patients in whom BTK pathway activity is elevated compared with people with ACPA-negative rheumatoid arthritis. Thus, compounds targeting BTK inhibition might elicit improved responses among patients with ACPA-positive disease. Such observations require further study to help identify people who might be able to benefit most from BTK inhibition.

Pharmacokinetic data were variable and inconsistent. Trough concentrations of BMS-986142 decreased over time, possibly due to autoinduction of the enzymes that metabolise the compound. In addition, varying baseline concentrations of these enzymes across individual participants, and potentially different levels of post-treatment autoinduction, might have contributed to the variability observed in the trough concentrations. As anticipated, trough concentrations of BMS-986142 increased in a dose-dependent manner. Of note, relative to half-maximal inhibitory concentrations, trough concentrations suggest little target engagement over the dosing interval, because near-complete BTK inhibition might be needed for optimal efficacy.[7] Furthermore, high interpatient variability in trough concentrations could have impacted on achieving consistent and sufficient dose-dependent inhibition of BTK. As a result, the desirable level of target inhibition needed for optimal efficacy might not have been achieved at the dose levels included. As a reversible, non-covalent BTK inhibitor, BMS-986142 does not provide continuous or maximal inhibition at the studied doses, and these data suggest a potential advantage for a covalent inhibitor that would continue to inhibit beyond the duration of parent

molecule pharmacokinetic exposure. However, several covalent inhibitors have not shown efficacy in patients with rheumatoid arthritis.[11,12] One potential explanation for the clinically observed effects is that the preclinical assessment of BTK inhibition for a particular compound might be an inaccurate representation of its inhibition in vivo, leading to an incorrect classification of partial or full BTK inhibitor.

The possibility that target inhibition was not optimal in this study is supported by the moderate but dose-dependent reduction of CXCL13 for the 200 mg group in this study, which was similar to the decline in CXCL13 seen in patients with rheumatoid arthritis receiving spebrutinib (375 mg per day), an irreversible, covalent BTK inhibitor.[11] Alternatively, ibrutinib (an irreversible, covalent BTK inhibitor) achieved a high degree of BTK occupancy (>90%) in patients with mantel cell lymphoma (560 mg per day), which was associated with a more robust CXCL13 response.[27] Importantly, CXCL13 is a selective chemokine for B cells that has a central role in positioning, organisation, and activation of cells at lymphoid and extra-lymphoid sites, and has emerged as a prognostic biomarker for patients with rheumatoid arthritis.[28–31] We observed an association between CXCL13 reduction and improved disease-activity scores, suggesting that a greater reduction of CXCL13, through improved BTK inhibition, might improve clinical response.

Post-hoc subgroup analyses showed a nominally significant ACR20 response for BMS-986142 200 mg versus placebo among ACPA-positive participants, although sample sizes were small. This observation, which has also been reported for rheumatoid arthritis therapies with other mechanisms of action, including rituximab,[32] is suggestive of a role for BTK inhibition on citrullinated protein-reactive B cells.[33] Consistent with our observation, fenebrutinib, a reversible non-covalent BTK inhibitor, showed efficacy in patients positive for both rheumatoid factor and ACPA,[10] supporting the idea that BTK inhibition might show better efficacy in individuals who are autoantibody-positive.

This study has notable strengths, such as the adaptive study design and interim analysis seeking to maximise patient risk–benefit ratio. Furthermore, a wide array of clinical, imaging, and soluble biomarker measures were assessed. Together, these novel evaluations advance our understanding of the mechanism of action of BTK inhibitors and highlight the importance of developing a BTK inhibitor with optimal characteristics. Despite such strengths, this study was limited by the inability to examine the highest dose due to the pre-specified interim analysis. In addition, some statistical limitations should be noted: trial groups did not reach the predefined sample size of 82 patients per group, and no adjustments for multiplicity were made for any of the analyses. Lastly, data with nominally significant p values are hypothesis-generating only and require adequately powered pre-specified endpoints for clinical assessment.

In general, the doses of BMS-986142 studied (100 mg and 200 mg) were well tolerated and had an acceptable safety profile. The co-primary endpoints were not met; overall, the findings support the contribution of BTK signalling to rheumatoid arthritis pathogenesis and symptoms, but further investigation of BMS-986142 in people with rheumatoid arthritis is not warranted. The absence of observed clinical benefit highlights the need for additional research to understand: (1) the extent of BTK inhibition via reversible or irreversible BTK inhibitors; (2) the effect of a longer duration of treatment than already studied; and (3) the adequacy of distribution to inflammation sites, in the utility of BTK inhibition as a therapeutic strategy for rheumatoid arthritis. Soluble biomarker data suggest insufficient inhibition of BTK with this reversible BTK inhibitor and highlight the importance of developing compounds that maximise BTK inhibition without safety concerns. In summary, these observations provide insights into the mechanism of action of BTK inhibition in rheumatoid arthritis and suggest that the development of future therapies designed to target BTK for mitigating disease-related symptoms in people with rheumatoid arthritis needs further consideration in the context of potential unknowns.

Contributors

PGC, MN, SD, IMC, an DMG were involved in study conception and design. MN, SD, YL, and IMC were responsible for data acquisition. PGC, MN, SD, YL, JL, CP, AF, IMC, DMG, and MØ were involved in the analysis and interpretation of data. PGC, MN, SD, YL, JL, CP, AF, IMC, and DMG directly accessed and verified the underlying data reported in the Article. All authors had full access to all data in the study, were involved in drafting the article or revising it critically for important intellectual content, and had final responsibility for the decision to submit for publication.

Declaration of interests

PGC reports speaker or consultancy fees from AbbVie, Bristol Myers Squibb, Eli Lilly, Galapagos, GlaxoSmithKline, Merck, Novartis, Pfizer, Regeneron, and UCB. MN, SD, YL, JL, CP, AF, and IMC are full-time employees of and shareholders in Bristol Myers Squibb. DMG is a full-time employee of, shareholder in, and has received travel support from Bristol Myers Squibb. MØ reports research grants from Amgen, Bristol Myers Squibb, Celgene, Merck, and Novartis; and speaker or consultancy fees from AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, Gilead, Hospira, Janssen, Merck, Novartis, Pfizer, and UCB.

Data sharing

The Bristol Myers Squibb full policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Requests for clinical trial data from qualified researchers with a clearly defined scientific objective will be considered after publication of the primary results. Sharing is subject to protection of patient privacy and respect for the patient's informed consent. Data considered for sharing can include non-identifiable patient-level and study-level clinical trial data, full clinical study reports, and protocols. In-scope proposals are sent to an Independent Review Committee (IRC) to review and provide the final decision on the requests. The IRC ensures that qualifying requests for patient-level data have a complete, consistent, and fair assessment. Before data are released, the researcher or researchers will be expected to sign the Vivli Data Use Agreement. Upon execution of an agreement, the de-identified or anonymised datasets, or both, will be available within the Vivli Research environment. Data requests can be submitted at https://vivli.org/ourmember/bristol-myers-squibb/.

Acknowledgments

We thank the patients and all the investigators who participated in the study. This study was funded by Bristol Myers Squibb. Professional medical writing and editorial assistance was provided by Ryan Miller at Caudex and was funded by Bristol Myers Squibb. PGC is supported in part by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre. The views expressed in this publication are those of the authors and not necessarily those of the UK National Health Service, the NIHR, Health Education England, or the Department of Health and Social Care.

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