Granulocyte-macrophage colony-stimulating factor neutralisation in patients with axial spondyloarthritis in the UK (NAMASTE): a randomised, double-blind, placebo-controlled, phase 2 trial

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Summary

Background Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine overproduced in several inflammatory and autoimmune diseases, including axial spondyloarthritis. Namilumab is a human IgG1 monoclonal anti-GM-CSF antibody that potently neutralises human GM-CSF. We aimed to assess the efficacy of namilumab in participants with moderate-to-severe active axial spondyloarthritis.

Methods This proof-of-concept, randomised, double-blind, placebo-controlled, phase 2, Bayesian (NAMASTE) trial was done at nine hospitals in the UK. Participants aged 18–75 years with axial spondyloarthritis, meeting the Assessment in SpondyloArthritis international Society (ASAS) criteria and the ASAS-defined MRI criteria, with active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were eligible. Those who had inadequately responded or had intolerance to previous treatment with an anti-TNF agent were included. Participants were randomly assigned (6:1) to receive subcutaneous namilumab 150 mg or placebo at weeks 0, 2, 6, and 10. Participants, site staff (except pharmacy staff), and central study staff were masked to treatment assignment. The primary endpoint was the proportion of participants who had an ASAS ≥20% improvement (ASAS20) clinical response at week 12 in the full analysis set (all randomly assigned participants). This trial is registered with ClinicalTrials.gov (NCT03622658).

Findings From Sept 6, 2018, to July 25, 2019, 60 patients with moderate-to-severe active axial spondyloarthritis were assessed for eligibility and 42 were randomly assigned to receive namilumab (n=36) or placebo (n=six). The mean age of participants was 39·5 years (SD 13·3), 17 were women, 25 were men, 39 were White, and seven had previously received anti-TNF therapy. The primary endpoint was not met. At week 12, the proportion of patients who had an ASAS20 clinical response was lower in the namilumab group (14 of 36) than in the placebo group (three of six; estimated between-group difference 6·8%). The Bayesian posterior probability η was 0·72 (>0·927 suggests high clinical significance). The rates of any treatment-emergent adverse events in the namilumab group were similar to those in the placebo group (31 *vs* five).

Interpretation Namilumab did not show efficacy compared with placebo in patients with active axial spondyloarthritis, but the treatment was generally well tolerated.

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Introduction

Axial spondyloarthritis is an immune-mediated inflammatory rheumatic disease—typically presenting in young adults—characterised by chronic inflammatory back pain, inflammation of the sacroiliac joints, spine, and sometimes peripheral joints, and substantial morbidity.[1] The prevalence of axial spondyloarthritis is approximately 0·5% of the general population.[1]

Current licensed pharmacological treatment options for patients with axial spondyloarthritis include non-steroidal anti-inflammatory drugs (NSAIDs), biological inhibitors of tumour necrosis factor (TNF) or IL-17A and IL-17F,[2–4] and oral Janus kinase (JAK) inhibitors (such as tofacitinib and upadacitinib).[5] However, despite the availability of various treatment options, around a third of patients do not reach clinically meaningful responses;[2–5] therefore, there is still a need for novel therapies for effective management of patients with axial spondyloarthritis.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine[6,7] overproduced in several inflammatory and autoimmune diseases,

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Research in context

Evidence before this study

Axial spondyloarthritis is an immune-mediated inflammatory disease with unknown pathogenesis. We searched PubMed for articles and clinical guidelines published from Jan 1, 2008, to Jan 1, 2018, using the terms "axial spondyloarthritis", "biologics", and "JAK". Previous clinical trial data showed that biological tumour necrosis factor (TNF) inhibitors, IL-17A inhibitors, and oral Janus kinase (JAK) inhibitors can result in meaningful clinical responses in patients with axial spondyloarthritis and are generally well tolerated. These inhibitors are suggested as treatment options by most rheumatology society guidelines, including those by the American College of Rheumatology, the Assessment in SpondyloArthritis international Society (ASAS), and the European Alliance of Associations for Rheumatology. However, these approved treatments do not provide meaningful clinical responses for around a third of patients, meaning that there is a need for novel therapies for patients with axial spondyloarthritis. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a proinflammatory cytokine overproduced by lymphoid cells in the blood and inflamed joints in those with axial spondyloarthritis; its neutralisation has shown efficacy in treating arthritis in the murine SKG model of spondyloarthritis and in clinical trials for patients with rheumatoid arthritis. These findings provide a rationale for GM-CSF neutralisation as a possible novel therapy for the treatment of patients with axial spondyloarthritis.

Added value of this study

To address this hypothesis, we conducted a proof-of-concept, randomised, double-blind, placebo-controlled, phase 2 trial with four subcutaneous injections of namilumab 150 mg or placebo administered over 10 weeks for 42 participants with moderate-to-severe active axial spondyloarthritis. Our findings show that namilumab was well tolerated but did not result in significant clinical improvement compared with placebo (as assessed by the ASAS20 response at week 12). No significant safety concerns were identified during the 28-week observation period.

Implications of all the available evidence

In this trial, namilumab did not show a therapeutic benefit compared with placebo at week 12 in patients with active axial spondyloarthritis. We cannot exclude that a higher dosing regimen might be efficacious.

including rheumatoid arthritis,[8,9] juvenile idiopathic arthritis,[10] and psoriatic arthritis (with genetic linkage).[11] We have previously shown enhanced GM-CSF production within inflamed joints in patients with peripheral spondyloarthritis by various lymphoid cells (including T cells and natural killer [NK] cells) and innate lymphocytes,[12] together with evidence that GM-CSF primes monocytes to produce enhanced inflammatory responses.[13] Furthermore, GM-CSF neutralisation has shown a benefit for lung disease and peripheral arthritis in the murine SKG model of spondyloarthritis.[14] These preclinical findings provide a rationale for GM-CSF neutralisation as a possible novel therapy for the treatment of patients with axial spondyloarthritis. Several monoclonal antibodies to GM-CSF or its receptor have been developed for human therapeutic trials. Namilumab is a human IgG1 monoclonal anti-GM-CSF antibody that potently and specifically neutralises human and macaque GM-CSF. Clinical studies have been completed with namilumab in patients with active rheumatoid arthritis who received treatment with methotrexate and in patients with psoriasis. Namilumab was reported to be generally safe and well tolerated and has shown efficacy for rheumatoid arthritis,[15,16] but not psoriasis.[17]

In patients with rheumatoid arthritis, namilumab was administered at 150 or 300 mg on days 0, 15, and 29 in the phase 1b PRIORA study[15] and at 20, 80, or 150 mg at weeks 0, 2, 6, and 10 after random assignment for those who had an inadequate response to methotrexate or TNF inhibitors in the subsequent phase 2 trial.[16] Based on preclinical data and the phase 2 study we hypothesised that namilumab would be a viable treatment for patients with axial spondyloarthritis.

Here, we aimed to assess the efficacy of namilumab, a biological GM-CSF inhibitor, on the clinical response in participants with moderate-to-severe active axial spondyloarthritis and whether GM-CSF inhibition should be further investigated in larger scale clinical trials as a novel therapy for this patient population.

See Online for appendix

For the **study protocol** see https://clinicaltrials.gov/ct2/show/NCT03622658

Methods

Study design and participants

This proof-of-concept, randomised, double-blind, placebo-controlled, phase 2, Bayesian (NAMASTE) trial was done at nine centres and hospitals in the UK (appendix p 6). This study was conducted in accordance with the Good Clinical Practice guideline and the Declaration of Helsinki. The study protocol was approved by the Oxford A research ethics committee (18/SC/0241) and is available online. This trial is registered with EudraCT (2018–000176–15) and ClinicalTrials.gov (NCT03622658).

Eligible participants aged 18–75 years had to have a physician-verified diagnosis of axial spondyloarthritis, fulfil Assessment in SpondyloArthritis international Society (ASAS) classification criteria, meet ASAS-defined MRI criteria for sacroiliac joint inflammation on an MRI done within 3 months before randomisation and no longer than 6 months after randomisation (when feasible),[18] and have active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

score of 4 or higher and spinal pain score of 4 or higher (both scores range 0–10) at screening and baseline. Stable doses of NSAIDs, low-dose corticosteroids, methotrexate, sulfasalazine, or leflunomide were permitted. Patients who had an inadequate response to, or had intolerance to, previous treatment with an anti-TNF agent were included but capped at 50% of the total study population. A complete list of inclusion and exclusion criteria is shown in the appendix (pp 1–2). Sex and gender data were self-reported by patients. All patients provided written informed consent.

Randomisation and masking

Participants were randomly assigned (6:1) to receive namilumab or placebo. At screening, participants were assigned a unique randomisation number using an interactive web response system, which was maintained by the statistics department of the contract research organisation (IQVIA, London, UK). The injection volume was identical between study groups but products were not visually identical. Unmasked clinical trial pharmacists applied a clear yellow label to the cover of the syringe before the drug product was drawn from the vial in the pharmacy aseptic unit. Participants, site staff (except pharmacy staff), and central study staff remained masked to treatment assignment throughout the study. Randomisation was stratified according to previous anti-TNF exposure. To avoid allocation bias, separate randomisation schedules were used within each study centre and weight class (ie, randomly permuted blocks within strata).

Procedures

The GM-CSF neutralising monoclonal antibody namilumab and a placebo solution were provided by the study funder (Izana Biosciences, on licence from Takeda) through Fisher Scientific (Pittsburgh, PA, USA). After a 4-week screening period, participants received 1·2 mL subcutaneous injection of namilumab 150 mg or placebo at the baseline visit (week 0) with subsequent doses of 150 mg administered at weeks 2, 6, and 10. Patients returned at week 12 (double-blind treatment evaluation period) for an end of treatment visit during which efficacy and safety assessments were done. Follow-up was conducted by telephone at week 18 and with an in-person assessment including additional safety at the end of study visit at week 28.

An independent internal data monitoring committee reviewed all safety events quarterly and reported to the trial management group and trial steering committee. Physical examinations, vital sign measurements, pulse oximetry,[19] and clinical laboratory testing were performed at each visit. Electrocardiograms were done at screening and at weeks 6, 10, and 12. To screen for pulmonary alveolar proteinosis, participants were monitored for symptoms of breathlessness with the Medical Research Council (MRC) dyspnoea scale[19] at all study visits. Participants were screened for neutropenia and myeloid suppression with a full blood count at study visits. Lung function tests were carried out at baseline and week 12 and chest x-rays were done at screening, week 12, and week 28.

MRI showing evidence of active axial spondyloarthritis (evaluated by a local radiologist) was mandatory before randomisation and study centres were encouraged to perform a MRI scan at week 12–16 after treatment. MRI was obtained using a scanner of at least 1·0 Tesla flux density. Sagittal images of the upper (including C2 to T10) and lower (including T8 to S1) spine and coronal oblique images of the sacroiliac joints were taken. The field of view was 34–38 cm. The following sequences were used: T1-weighted turbo spin echo with a slice thickness of 3 mm and short tau inversion recovery (STIR; a sequence with intrinsic fat saturation) with a slice thickness of 3 mm. MRI assessments followed a standardised scanning method with Coronal oblique T1-weighted (T1) Coronal oblique STIR/proton-density fat-suppressed (PD FS) and Axial PD FS or STIR. The exact parameters for the scanning protocols varied between institutions. Paired scans were sent for central reading imaging and evaluated independently by two experienced investigators (PMM and JT) who were masked to clinical details, treatment allocation, and chronology of images. MRI scans were evaluated using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index for scoring inflammation of the spine and sacroiliac joints.[20] The mean of both readers' scores were used in the analysis. In case of discrepancy between the two central readers, a consensus was reached by discussion.

Outcomes

The primary endpoint was the proportion of participants who had an ASAS ≥20% improvement (ASAS20) clinical response at week 12. Secondary endpoints were the proportion of participants who had ASAS ≥40% improvement (ASAS40) clinical response at week 12, proportion of participants who had an ASAS20 clinical response at week 6, and Ankylosing Spondylitis Disease Activity Score (ASDAS; based on C-reactive protein [CRP])[21,22] responses at weeks 6 and 12. ASDAS clinically important improvement (a decrease from baseline ASDAS ≥1·1) and major improvement (a decrease from baseline ASDAS ≥2·0) were calculated. ASAS responders are defined as the patients with at least three of the four domains collected in the electronic case report form and no worsening in the fourth domain: patient's Global Assessment of Disease Status, patient's assessment of Spinal Pain, function (BASDAI) and inflammation (last two questions of the BASDAI).

Prespecified exploratory endpoints were the proportion of patients who had ASAS20 clinical responses at weeks 2 and 10; the proportion of patients with ASDAS clinical responses at weeks 2 and 10; 66/68 Swollen and

Tender Joint Counts; Leeds Enthesitis Scores (assessed by study physicians);[23] participants' assessments of global disease activity and spinal pain severity (both measured by a 100 mm visual analogue scale); BASDAI;[24] Bath Ankylosing Spondylitis Functional Index[25] at weeks 0, 2, 6, 10, and 12; and neuropathic pain scoring (painDETECT questionnaire)[26] at weeks 6 and 12. Only week 6 and week 12 data for ASAS20 and ASDAS are shown in this manuscript for brevity. Prespecified exploratory objectives to assess the efficacy of namilumab included radiological MRI responses and laboratory measures. Routine safety evaluations included monitoring of treatment-emergent adverse events, defined as events with onset or worsening after the first dose of the study drug. Selected treatment-emergent adverse events of special interest were pulmonary alveolar proteinosis, neutropenia, and myeloid suppression.

Statistical analysis

The study used a Bayesian approach which uses information from previous studies to determine the sample size and probability (appendix p 3). The placebo prior of β(p=0·3, n=20), and the prior for namilumab of β(p=0·6, n=5)—ie, a 30% placebo and 60% namilumab treatment response was supposed.

The sample sizes are the smallest number of participants such that the median Q(P{θnamilumab > θplacebo| Y(HA)}, 1−γ) > Q(P{θnamilumab > θplacebo| Y(H0)}, γ), where Q(f, γ) represents the γ quantile from the distribution f, Y(HA) represents data generated under the alternative hypothesis, and Y(H0) represents data generated under the null hypothesis. Based on γ=0·9, a sample size of 42 participants was estimated to have a power of 90% to detect namilumab efficacy on ASAS20 in the Bayesian study design. The α level used for the sample size calculation was 0·1 (=1−γ; where γ=0·9).

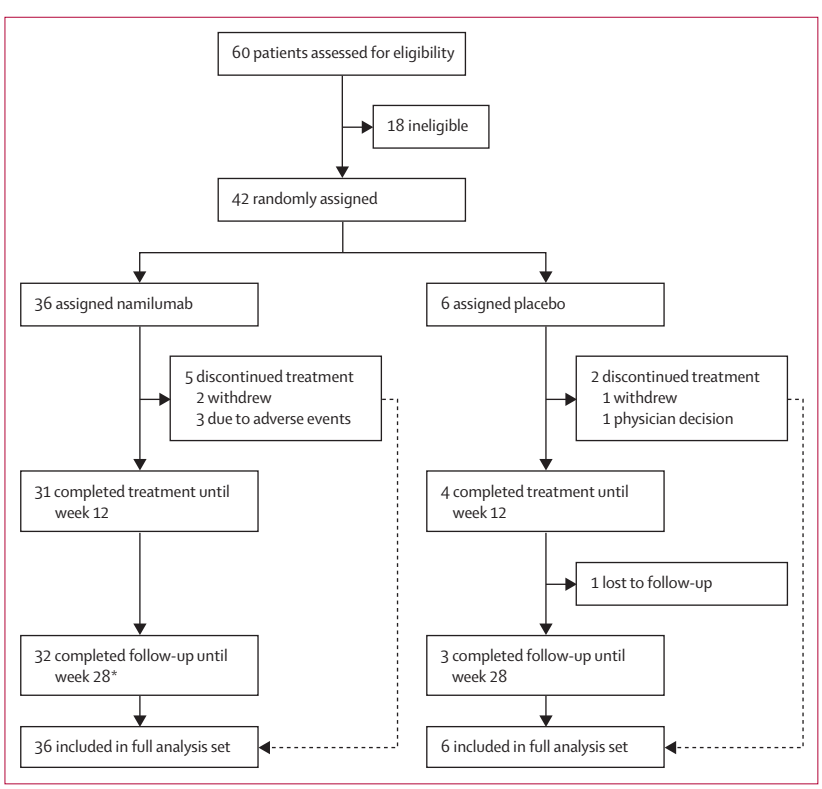

Figure 1: **Trial profile**
*Including one patient who did not complete namilumab treatment, but continued safety follow-up.

Efficacy for all primary and secondary endpoints was assessed in all randomly assigned patients who received at least one dose of the study drug and were grouped according to assigned treatment (full analysis set). Safety was assessed in all randomly assigned patients who received at least one dose of study drug and were grouped according to the actual treatment received (safety analysis set).

The primary aim of this study was to test the hypothesis that there is no difference in the proportion of ASAS20 responders between the namilumab and placebo groups. H0: $\pi_{namilumab}=\pi_{placebo}$, where π represents the ASAS20 responder rate.

The primary endpoint was assessed using a Bayesian analysis on the full analysis set. The control group had a β prior with a parameter rate of 0·3 and ν=20, and the namilumab group had a β prior with a rate of 0·6 and ν=5. The parameterisation used here is beta (α, β), where rate is α/ν and ν=α+β, and the density of beta (α, β) is proportional to $x^{\alpha}(1-x)^{\beta}$. Posterior distributions were calculated using simulation (100 000 random draws) and programmed random occurrence Markov chain Monte Carlo to calculate the posterior estimates. The parameter distributions (estimated rates and rates difference) and 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the posterior distribution are shown for the proportion of patients with ASAS20 clinical response at week 12. The sample size was the smallest sample size so that P{θnamilumab>θplacebo| Y(HA)}>0·927 with probability 0·9, assuming true response rates of 0·3 for the control group and 0·6 for the namilumab group. Given the observed data, the posterior probability $\eta \equiv P(\pi_{namilumab} > \pi_{placebo})$ was calculated. Values of η>0·927 provide strong evidence that namilumab has a therapeutic benefit compared with placebo.

Secondary endpoints (ASAS20 at week 6 and ASAS40 at week 12) were also analysed using a Bayesian approach (at the request of a reviewer instead of the planned frequentist Fisher's exact test). A non-informative normal prior was assumed for the log odds ratio (logOR) with hyperpriors for the mean of normal (0,1000^2). Correspondingly, a normal likelihood for the logOR was used. A correction of 0·5 was added to each cell for calculating the point estimate and variance of the logOR if needed to calculate the OR due to a zero value.[27] A prespecified sensitivity analysis applied the same model—except with a mildly informative prior—for the logOR normal (0,2^2) equivalent to 95% of the prior distribution for OR between 1/50 and 50. The median OR and 95% credible intervals were calculated

	Namilumab (n=36)	Placebo (n=6)
Age, years	40·0 (13·9)	36·3 (9·2)
HLA-B27+		
Positive	29	3
Negative	5	2
Missing data	2	1
Duration of disease*		
<2 years	16	4
≥2 years	20	2
Median disease duration, years	2·5 (0·4–8·9)	1·5 (0·6–4·3)
Sex		
Male	21	4
Female	15	2
Race		
White	34	5
Black or African American	0	0
Asian	0	1
American Indian or Alaska Native	0	0
Native Hawaiian or Pacific Islander	0	0
Multiple	1	0
Other	1	0
Ethnicity		
Hispanic or Latino	0	1
Not Hispanic or Latino	33	5
Missing data	3	0
Height, cm	173·4 (9·7)	173·0 (7·4)
Weight, kg	83·6 (18·6)	82·1 (15·5)
BMI, kg/m²	27·8 (5·5)	27·5 (5·3)
Previous use of anti-TNF treatment	6	1
Median C-reactive protein mg/L at randomisation	7·1 (2·6–13·1)	7·4 (5–16)
(Continued from previous column)		
C-reactive protein ≥6 mg/L at randomisation	19	4
ASAS-defined MRI criteria for sacroiliac joint inflammation on MRI†	36	6
Previous or current skin psoriasis	2	1
Previous or current uveitis or iritis	4	0
Previous or current inflammatory bowel disease	0	0
Median tender 66 joint count	2 (1–4)	1 (0–4)
Median swollen 66 joint count	0 (0–0)	1 (0–2)
Swollen 66 joint count ≥1	7	3
Median Leeds Enthesitis score	1 (0–2)	0 (0–2)
Ankylosing Spondylitis Disease Activity Score C-reactive protein‡		
≥2·1 and <3·5 (high disease activity)	14	1
≥3·5 (very high disease activity)	21	5
Patient's assessment of spinal pain on visual analogue scale (0–100)	67·5 (13·9)	82·2 (8·0)
Bath Ankylosing Spondylitis Disease Activity Index	64·7 (13·1)	77·7 (11·1)
Bath Ankylosing Spondylitis Functional Index	51·3 (20·2)	62·3 (18·7)

Data are mean (SD), median (IQR), or n. ASAS=Assessment of SpondyloArthritis international Society. HLA=human leukocyte antigen. TNF=tumour necrosis factor. *Time from initial diagnosis until first dose (calculated to the nearest month where available). †MRI was done when feasible within 3 months before randomisation and no longer than 6 months after randomisation. ‡n=35 in the namilumab group.

Table 1: **Patient demographics and baseline characteristics**

from the respective posterior distribution. The WinBUGS programme (version 1.4.3) was used with 1000 burn-in and 10 000 iterations. The other secondary endpoints and prespecified exploratory efficacy endpoints were analysed descriptively and no hypothesis testing was performed. No imputation for missing data was used for the exploratory endpoints, except for the endpoints related to ASAS and ASDAS. For these, any patient with missing data at the timepoint of interest was considered a non-responder. The number and percentage of patients who had treatment-emergent adverse events were tabulated using the Medical Dictionary for Drug Regulatory Activities (version 21.0).

Role of the funding source

The funder of the study had a role in study design, data analysis, data interpretation, and approving of the report.

Results

From Sept 6, 2018, to July 25, 2019, 60 patients with moderate-to-severe active axial spondyloarthritis were assessed for eligibility, 18 of whom were ineligible (figure 1). 42 participants were randomly assigned: 36 to receive namilumab and six to receive placebo. The mean age of participants was 39·5 years (SD 13·3), 17 were women, 25 were men, 39 were White, and 20 had a disease duration of less than 2 years (table 1). Seven patients previously received anti-TNF therapy. A detailed schematic of the study design is shown in the appendix (p 12).

All 42 participants received at least one dose of the study drug (full analysis set) and 35 completed the study as per protocol (ie, completed follow-up until week 28; 31 of 36 in the namilumab group and four of six in the placebo group). Five participants in the namilumab group discontinued study treatment early (three due to adverse events and two withdrew) compared with two in the placebo (one withdrew and one physician decision).

The primary endpoint was not met. At week 12, the proportion of patients who had an ASAS20 clinical response was lower in the namilumab group (14 of 36) than in the placebo group (three of six; table 2). The estimate of the ASAS20 responder rate by posterior distribution was 41% for the namilumab group and 35% for the placebo group (estimated between-group

	Namilumab (n=36)	Placebo (n=6)	Namilumab – placebo
ASAS20 responders*	14	3	..
ASAS20 non-responders*	22	3	..
Endpoint missing*	4	1	..
Posterior distribution†			
Estimate of ASAS20 responders rate*†	41·40%	34·60%	6·80%
Fifth percentile	29·19%	20·35%	–12·90%
10th percentile	31·72%	23·09%	–8·52%
25th percentile	36·14%	28·10%	–1·12%
50th percentile	41·33%	34·17%	6·99%
75th percentile	46·59%	40·69%	14·99%
90th percentile	51·29%	46·66%	22·00%
95th percentile	54·09%	50·29%	26·01%
Posterior probability‡	..	..	0·72

ASAS20=Assessment of SpondyloArthritis international Society ≥20% improvement. *Patients with missing week 12 data were imputed as non-responders. †The primary endpoint (ASAS20) was assessed using a Bayesian analysis. The placebo group has a β prior with parameter rate of 0·3 and v=20, and the namilumab group has a β prior with rate of 0·6 and v=5. ‡Given the observed data, the posterior probability was calculated using $\eta \equiv P(\pi_{namilumab} > \pi_{placebo})$ and an η of more than 0·927 provides strong evidence that namilumab has a therapeutic benefit compared with the placebo.

Table 2: **Efficacy results for the primary endpoint in the full analysis set**

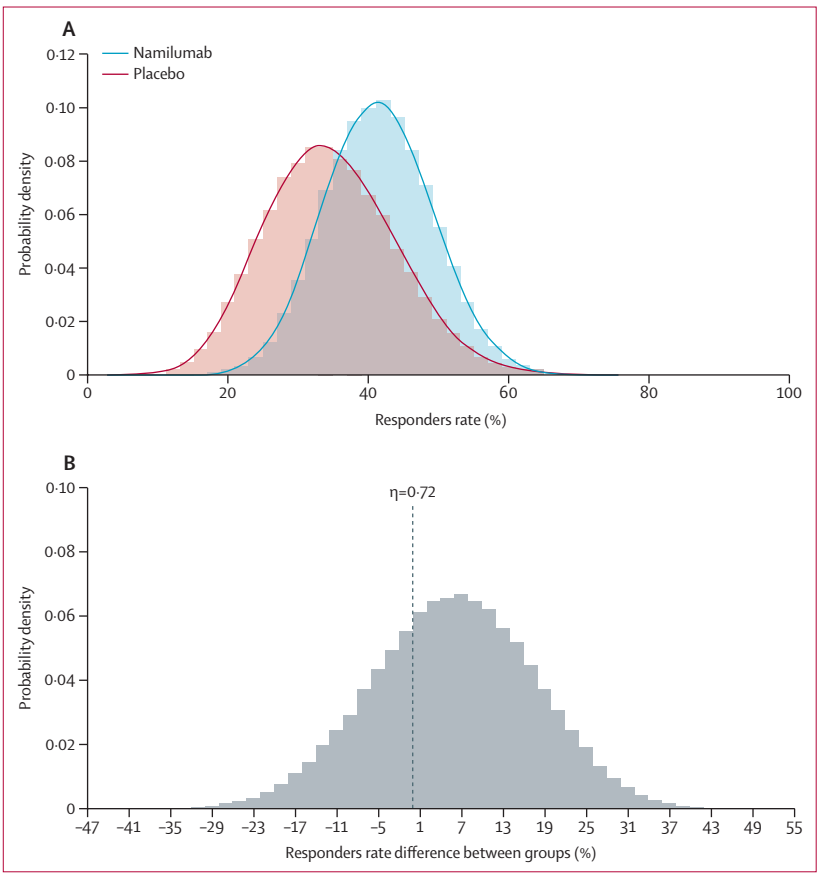

Figure 2: **Proportion of patients with ASAS20 clinical response at week 12 in the full analysis set**
ASAS20=Assessment of SpondyloArthritis international Society ≥20% improvement.

difference 6·8%; figure 2; appendix p 36). These data yielded a posterior probability η of 0·72, which does not provide evidence that namilumab has a therapeutic benefit.

Results for selected key secondary efficacy endpoints, including ASAS20 responders at week 6 and ASAS40 responders at week 12 are summarised in table 3. There was some evidence in favour of namilumab at week 6 for ASAS20 (12 *vs* none in the placebo group; table 3), but not at week 12 for ASAS40. Other ASDAS responses at weeks 6 and 12 are shown in the appendix (p 7). At week 6, ten of 33 patients in the namilumab group versus none in the placebo group reached clinically important improvements in ASDAS and two versus none reached major improvements in ASDAS (appendix p 7).

In terms of prespecified exploratory endpoints, no statistically significant changes between namilumab and placebo groups were seen in CRP, 66/68 Swollen and Tender Joint Counts, or Leeds Enthesitis Scores (appendix p 8). The neuropathic painDETECT scores were similar for namilumab versus placebo at baseline (median 11·5 [IQR 7·5–17·0] *vs* 13·0 [8·0–14·0]), week 6 (8·0 [6·0–12·0] *vs* 8·0 [5·0–9·0]), and week 12 (7·0 [4·0–14·0] *vs* 11·0 [8·0–12·0]; appendix p 9).

Of the 15 patients for whom paired MRI scans were available (all in the namilumab group), eight showed improvement in SPARCC inflammation scores and seven showed no change or deterioration. The mean change in SPARCC score from baseline to end of treatment was –4·8 (range –30·5 to 33·0 [SD 14·3]).

Five patients in the namilumab group and two in the placebo group had protocol deviations, all of which were categorised as major and were due to missing week 12 efficacy data. These protocol deviations are not believed to have influenced the overall conclusions related to safety or efficacy as values remained within the quality tolerance limit for the namilumab group. Results for the following prespecified exploratory endpoints are not shown: ASAS20 and ASDAS clinical responses at weeks 2 and 10; participants' assessments of global disease activity and spinal pain severity; BASDAI; and Bath Ankylosing Spondylitis Functional Index at weeks 0, 2, 6, 10, and 12.

The rates of any treatment-emergent adverse events in the namilumab group were similar to those in the placebo group (31 *vs* five; table 4). A similar proportion of patients in the namilumab and placebo groups (19 *vs* three) had a treatment-emergent adverse event considered by the investigator to be related (probably or possibly) to the study treatment. Severe treatment-emergent adverse events were reported for four patients in the namilumab group and none in the placebo group. Three patients in the namilumab group had one or more treatment-emergent adverse event that led to permanent discontinuation of study treatment. These were duodenitis (one patient), road traffic accident (one patient), dyspnoea (one patient), flare of axial spondyloarthritis (one patient).

One patient reported dyspnoea but detailed specialist pulmonary assessment including high-resolution CT found no evidence of pulmonary alveolar proteinosis or other pulmonary disease.

There were no serious related treatment-emergent adverse events, adverse events of special interest, or deaths during the study. Blood chemistry and haematology variables were similar between study groups and stable throughout the study duration. Key laboratory values are summarised in the appendix (pp 10–11). No patient discontinued the study due to atypical laboratory results. MRC dyspnoea score and lung function tests were similar in both study groups and stable from baseline to week 12 (data not shown). Mean pulse oximetry was also similar and stable over the course of the study, and oxygen saturation measured more than 96% in both study groups at all timepoints.

	Namilumab (n=36)	Placebo (n=6)	Median odds ratio (95% credible interval)
Week 6 visit			
ASAS20 responder	12	0	..
ASAS20 non-responder	24	6	..
ASAS20 missing*	3	1	..
Non-informative prior	..	..	25·50 (1·30–498·00)
Mildly informative prior (prespecified sensitivity analysis)	..	..	7·89 (0·73–85·00)
Week 12 visit			
ASAS40 responder	9	3	..
ASAS40 non-responder	27	3	..
ASAS40 missing*	4	1	..
Non-informative prior	..	..	0·33 (0·06–1·98)
Mildly informative prior (prespecified sensitivity analysis)	..	..	0·40 (0·08–2·03)

ASAS=Assessment of SpondyloArthritis international Society. *Patients with missing data were designated as non-responders.

Table 3: **Selected key secondary efficacy endpoints in the full analysis set**

	Namilumab (n=36)	Placebo (n=6)
Any treatment-emergent adverse event*	31	5
Related treatment-emergent adverse event†	19	3
Severe treatment-emergent adverse event	4	0
Serious treatment-emergent adverse event	1	0
Serious related treatment-emergent adverse event†	0	0
Treatment-emergent adverse event leading to permanent discontinuation of study treatment	3	0
Treatment-emergent adverse event of special interest	0	0
Treatment-emergent adverse event leading to death	0	0

*Defined as any adverse event with a start date on or after the first dose and within 125 days after the last dose. †Those classified as possibly related, probably related, or unknown relation were counted as related to the study treatment.

Table 4: **Safety summary in the full analysis set**

Discussion

In this phase 2 trial, we did not show efficacy of GM-CSF blockade in patients with moderate-to-severe active axial spondyloarthritis. The primary endpoint (the proportion of patients who had an ASAS20 clinical response at week 12) was not met and namilumab did not show a therapeutic benefit compared with placebo. Patients who previously received TNF inhibitors were included in the trial but were stratified equally between groups and did not influence the results. Notably, this study showed a substantial response rate among patients in the placebo group; with three of six having an ASAS20 clinical response at week 12. This finding was observed across study sites and the three placebo responders were enrolled at three different study sites (Oxford University Hospitals NHS Foundation Trust, Oxford, UK; University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; and Royal Berkshire NHS Foundation Trust, Reading, UK).

The effect of namilumab on ASAS20 clinical response at earlier timepoints was investigated in secondary (week 6) and prespecified exploratory analyses (weeks 2 and 10; data not shown) and did not show a benefit of namilumab versus placebo on ASAS20 or other exploratory efficacy endpoints (including swollen joint count, enthesitis, CRP, erythrocyte sedimentation rate [part of laboratory measures; appendix p 44], and painDETECT scores). At weeks 2 and 6, change from baseline ASDAS score (secondary endpoint) showed a positive effect for namilumab versus placebo, diminishing by weeks 10 and 12. This result suggests a possible benefit of GM-CSF inhibition in a subgroup of patients during the loading dose period (weeks 0–6) of the study; therefore, we cannot exclude the possibility that clinical efficacy might be reached with higher doses of namilumab, and more complete blockade of the GM-CSF ligand. Further clinical trials with higher doses of namilumab and immunological assays to test for completeness of target engagement in an appropriately powered study might be able to test this hypothesis. Follow-up MRI scans were included as a prespecified exploratory outcome in a subset of patients. No significant radiological response was observed, although only 15 paired MRI scans were available before and after treatment for central reading, which is a limitation of this study.

Four subcutaneous injections of namilumab 150 mg given for 10 weeks as therapy in patients with moderate-to-severe active axial spondyloarthritis, including those with an inadequate response previously or intolerance to anti-TNF therapy, was safe and well tolerated during this study. These findings are consistent with previous studies of namilumab, which also reported that the similar dosing regimen was safe and tolerable.[15,16]

The finding that GM-CSF neutralisation did not provide a clinical benefit for patients with axial spondyloarthritis was somewhat unexpected given the evidence of enhanced GM-CSF production in axial spondyloarthritis joints and efficacy in the preclinical murine SKG disease model. This finding is similar to the negative results reported with IL-23 and IL-6 neutralisation in patients with spondyloarthritis and might reflect the relative importance of different cytokines at various disease stages and in different tissues.[28–30]

The small sample size of the placebo group for this Bayesian study design represents a potential limitation in terms of similarity of baseline characteristics and sensitivity to sampling variability. Although the study groups were generally similar in demographic and baseline characteristics, the proportion of patients with a duration of disease of less than 2 years was lower in the namilumab group than in the placebo group. If this difference had an influence on the study findings, we would expect that patients with shorter disease duration might respond more favourably to an efficacious intervention, but this assumption was not the case. The large median ORs with wide corresponding credible intervals for the secondary efficacy outcomes reflect the small number of corresponding events and non-events; these results should be viewed cautiously (particularly the estimate of ASAS20 at week 6, given the corresponding sensitivity analysis result). Another limitation of our study was that five patients randomly assigned to namilumab and two randomly assigned to placebo did not complete the study, although reasons for discontinuation were similar for both groups. The possibility of bias due to random confounding is also an important limitation. Potential methodological limitations of this study include the measurement bias, selection bias in per-protocol estimates, and selection bias due to missing outcome data.

Finally, although our study was adequately powered to detect efficacy on the basis of expected placebo response rates from previous studies, we observed an unusually high proportion of responders at week 12 in the placebo group with a small sample size. Notably, the observed ASAS20 response rate in the namilumab group is also lower than that observed in trials of subsequently licensed therapies for patients with axial spondyloarthritis; therefore, we do not consider any of the mentioned limitations to have affected the study conclusions. This study did not show a therapeutic benefit of subcutaneous namilumab for patients with axial spondyloarthritis.

Contributors

PB, PCT, MHA-M, THC, and PMM contributed to the study design. PB, CW, MHA-M, PMM, JM, KG, NG, AC, JP, BAF, RS, and JT contributed to data acquisition. PB, PCT, CW, MHA-M, JAC, and THC contributed to data interpretation. CW, PB, and PCT were responsible for verifying the underlying data and have accessed and verified all the data in the study. All authors drafted the initial manuscript, approved the final draft, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

CW received funding from the Arthritis Therapy Acceleration Program (grant KENN161704) and Izana Bioscience. MHA-M holds stocks in GSK, UCB, and AstraZeneca; is an employee of AstraZeneca; and was an employee of UCB. BAF has received research funding from Janssen, Galapagos, and Celgene; and consultation fees from Novartis, Galapagos, Servier, Janssen, Roche, Sanofi, Bristol Myers Squibb, and UCB. AC has received payment or honoraria from Novartis, UCB, Amgen, AbbVie, and Janssen; and support for attending meetings or travel (or both) from Eli Lilly, UCB, and Novartis. RS has received research funding from Celgene and Novartis; payment or honoraria from AbbVie, Biogen, Eli Lilly, MSD, Novartis, Roche, and UCB; support for attending meetings or travel (or both) from AbbVie, Novartis, Eli Lilly, and UCB; participated on a data safety monitoring board or advisory board for AbbVie, Novartis, Eli Lilly, and UCB; is part of a chairmanship of trustees for the British Society for Spondyloarthritis and a trustee of the Bath Institute for Rheumatic Diseases. JP is a member of the executive committee of the British Society for Spondyloarthritis. KG has received research funding from Biogen, AbbVie, Pfizer, Novartis, Eli Lilly, Celltrion, Janssen, and Gilead; consulting fees from AbbVie, Novartis, UCB, and Eli Lilly; honoraria from AbbVie, Novartis, UCB, and Eli Lilly; and support for attending meetings or travel (or both) from Novartis, UCB, and Eli Lilly. NG has received research funding from Izana Bioscience, AbbVie, AstraZeneca, Eli Lilly, and Novartis; consulting fees from AbbVie, Novartis, and UCB; and payment or honoraria from AbbVie, Eli Lilly, Janssen, Novartis, and UCB; support for attending meetings or travel (or both) from AbbVie, Eli Lilly, UCB, and Novartis; receipt of equipment, materials, drugs, medical writing gifts, or other services from Eli Lilly and Novartis. THC was a chief medical officer at Izana Bioscience, received salary and stock options from Izana Bioscience, and participated in data safety monitoring board meetings. PMM has received consulting or speakers fees from AbbVie, BMS, Celgene, Eli Lilly, Galapagos, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB; and is supported by the National Institute for Health Research (NIHR), University College London Hospitals, and Biomedical Research Centre (BRC). PCT has received research funding from Galapagos and Izana Bioscience; consulting fees from AbbVie, Biogen, Galapagos, Gilead, GSK, Janssen, Eli Lilly, Pfizer, Sanofi, Nordic Pharma, Fresenius, UCB, and Izana Bioscience; payment or honoraria from AbbVie; support for attending meetings or travel (or both) from Eli Lilly; and participated on data safety monitoring boards for Kymab and Immunovant. PB has received research funding from Regeneron, BenevolentAI, GSK, and Novartis. JM, JAC, and JT declare no competing interests.

Data sharing

Deidentified summary data are available upon reasonable request to the corresponding author and after ethical approval.

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