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CLINICAL SCIENCE

Efficacy and safety of brodalumab, an anti-IL17RA monoclonal antibody, in patients with axial spondyloarthritis: 16-week results from a randomised, placebo-controlled, phase 3 trial

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ABSTRACT

Objective To investigate the efficacy and safety of brodalumab, a fully human anti-interleukin-17 receptor A monoclonal antibody, in patients with axial spondyloarthritis (axSpA).

Methods In a multicentre, placebo-controlled phase 3 study (NCT02985983) conducted at 48 sites across Japan, Korea and Taiwan, patients with axSpA were randomised 1:1 to receive subcutaneous brodalumab 210 mg (n=80) or placebo (n=79) at baseline, weeks 1 and 2 and every 2 weeks thereafter, during the 16-week double-blind period. The primary endpoint was the proportion of patients with Assessment of SpondyloArthritis International Society (ASAS) 40 response at week 16. Secondary endpoints included the proportion of patients with ASAS 20 response and change in Ankylosing Spondylitis Disease Activity Score using C-reactive protein (ASDAS-CRP) at week 16 and safety.

Results ASAS 40 response rate (n/N; 95% CI) was 43.8% (35/80; 32.7, 55.3) with brodalumab vs 24.1% (19/79; 15.1, 35.0) with placebo (rate difference, 19.7% (5.3, 34.1); p=0.018 by stratified Cochran-Mantel-Haenszel test). ASAS 20 response rate (n/N; 95% CI) was 67.5% (54/80; 56.1, 77.6) vs 41.8% (33/79; 30.8, 53.4) and least squares mean change (95% CI) from baseline (brodalumab, 2.660; placebo, 2.716) in ASDAS-CRP was -1.127 (-1.322, -0.931) with brodalumab vs -0.672 (-0.872, -0.473) with placebo at week 16. Treatment-emergent adverse events were reported in 44 (55%) and 45 (57%) patients in the brodalumab and placebo groups, respectively.

Conclusion Brodalumab demonstrated a significant improvement at week 16 in patients with active axSpA. Safety of brodalumab was consistent with that reported in previous global/Japanese psoriasis studies.

INTRODUCTION

Axial spondyloarthritis (axSpA) is an inflammatory disease characterised by chronic (≥ 3 months) back pain with an age at onset of < 45 years and both articular and extra-articular clinical manifestations.¹⁻³ Based on the Assessment of SpondyloArthritis International Society (ASAS) 2009 classification criteria,¹ axSpA was proposed as a single entity with two subtypes: ankylosing spondylitis (AS; radiographic axSpA) and non-radiographic axSpA (nr-axSpA).

Key messages**What is already known about this subject?**

- Interleukin (IL)-17 cytokines play a pathophysiological role in axial spondyloarthritis (axSpA), and clinical trials have demonstrated the efficacy and safety of IL-17 inhibitors in the treatment of ankylosing spondylitis (AS) and non-radiographic axSpA.
- Brodalumab is a novel IL-17 inhibitor that inhibits IL-17 by blocking IL-17 receptor A (IL-17RA).

What does this study add?

- Brodalumab demonstrated a significantly higher Assessment of SpondyloArthritis International Society 40 response rate at 16 weeks vs placebo, with a rate difference of 19.7%, and was well tolerated in patients with axSpA.
- The efficacy and safety of brodalumab was comparable with that previously demonstrated by other IL-17 inhibitors in patients with axSpA.

How might this impact on clinical practice or future developments?

- Short-term results from this study indicate that brodalumab, a novel IL-17RA inhibitor, can be a potential therapeutic option for patients with axSpA.

The worldwide prevalence of SpA is 0.1%–1.4%,^{4 5} with an estimated pooled prevalence of 0.2% in South-East Asia.⁶ AS affects 9–30 individuals/10 000 general population.⁷ A 2018 epidemiological survey reported ~3200 AS cases in Japan.⁸ Overall, 54 857 (in 2010)⁹ and 27 419 (in 2015)¹⁰ AS cases were identified from health insurance databases in Taiwan and Korea, respectively. The prevalence of nr-axSpA remains unreported.¹¹

Interleukin (IL)-17 cytokines play a pathophysiological role in axSpA.¹² Clinical trials have demonstrated the efficacy and safety of IL-17 inhibitors in the treatment of AS¹³⁻²³ and nr-axSpA.²⁴ Inhibition of IL-17A and IL-17F prevents inflammation and pathological and new bone formation.^{25 26} Brodalumab, a fully human anti-IL-17 receptor A (IL-17RA) monoclonal antibody, inhibits the activity of several other cytokines (IL-17A/F, IL-17C and

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IL-17E), including IL-17A and IL-17F, thus demonstrating a broader inflammation-blocking activity than other selective IL-17 inhibitors.²⁷ Brodalumab 210 mg is approved for the treatment of plaque psoriasis in North America, Canada, Europe,^{28 29} Japan³⁰ and other Asian countries. This phase 3 study aimed to evaluate the efficacy and safety of brodalumab in patients with active axSpA, including those with nr-axSpA. Here, we report the interim analysis efficacy and safety results of brodalumab vs placebo from the 16-week double-blind randomised period.

METHODS

Study design

This multicentre, randomised, placebo-controlled study, conducted at 48 sites across Japan (n=25), Korea (n=12) and Taiwan (n=11) from October 2016 to December 2019, comprised a 16-week double-blind period and a 52-week open-label extension period. An interim analysis was performed at week 16, following data cut-off, after all patients had completed their week 16 visit. Eligible patients were randomised 1:1 to receive subcutaneous brodalumab 210 mg (the dosage approved for psoriasis³⁰) or placebo at baseline, weeks 1 and 2 and every 2 weeks thereafter. Use of analgesics, such as acetaminophen and tramadol, and temporary dose increase or initiation of non-steroidal anti-inflammatory drugs (NSAIDs) during disease flare-ups were permitted at the physicians' discretion, except during 12 hours before a scheduled efficacy evaluation (excluding the screening test). NSAIDs were discontinued or their dose reduced upon flare-up resolution. Patients continuing conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or oral corticosteroids started before study enrolment maintained a stable dose during the 16-week study period.

Randomisation and masking

Patients were randomised to treatment groups in the order of enrolment using an interactive web response system (IWRS) by dynamic allocation and stratified based on baseline C-reactive protein (CRP) level (\geq / $<$ upper limit of normal (ULN)), region (Japan/Korea/Taiwan), disease subpopulations (AS/nr-axSpA) and informed consent (IC) for pharmacokinetic (PK) additional sampling (yes/no). Parexel International Inc. created a master randomisation list and allocated the study drug using the IWRS according to a prior written procedure. Investigators, patients' assessors, other study site personnel and the sponsor's representatives remained blinded until week 16, and the randomisation list was unblinded at the end of the double-blind period after all the patients had completed their week 16 visit.

All study participants provided written voluntary IC. The study was designed and sponsored by Kyowa Kirin and is registered at ClinicalTrials.gov (NCT02985983) and conducted after consultation and in agreement with the Japanese regulatory authorities.

Patient and public involvement

Patients or the public were not involved in the design or conduct or reporting or dissemination plans of our research.

Patients

Eligible patients included adults (aged ≥ 18 years), diagnosed as having axSpA by rheumatologists, meeting the ASAS classification criteria for axSpA (online supplemental table S1).¹ AS was diagnosed based on radiographic evidence of sacroiliitis grade ≥ 2 bilaterally or grade 3–4 unilaterally and ≥ 1 SpA

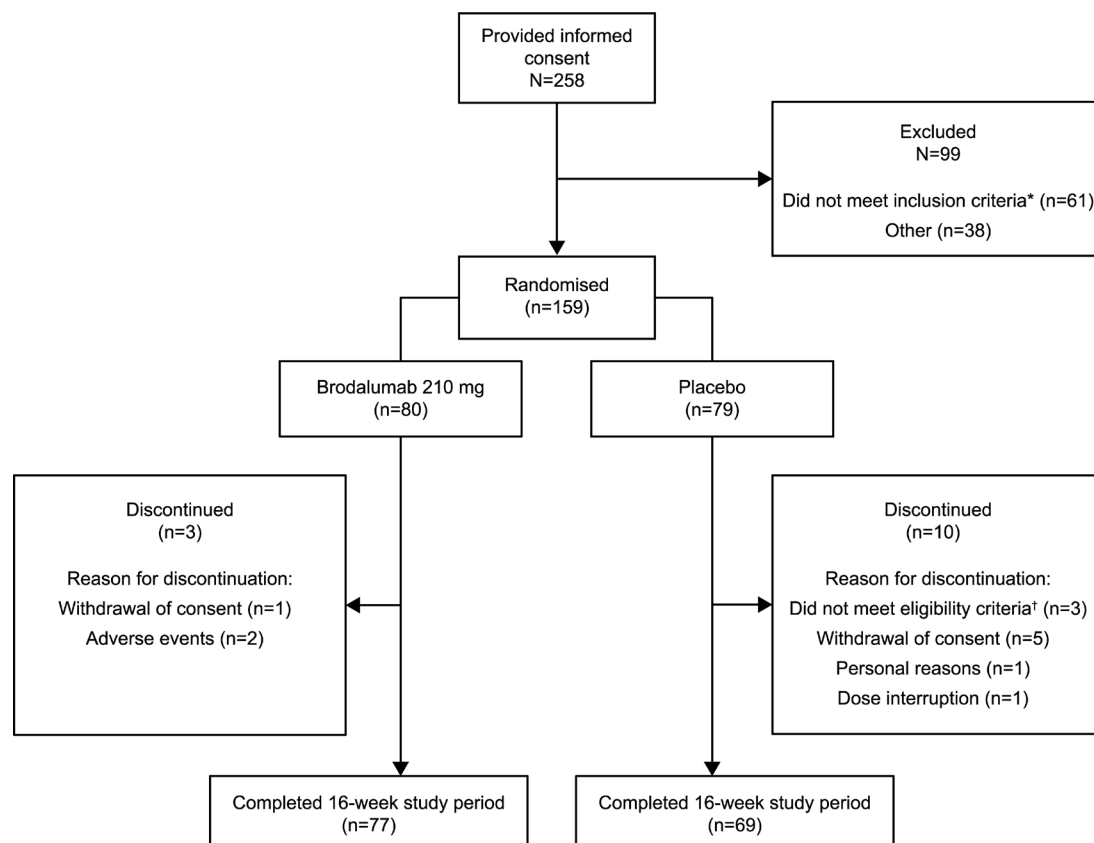


Figure 1 Patient disposition. *Did not meet the study criteria for AS or nr-axSpA, as judged by the central image readers. †Failed to meet the inclusion criteria or met one of the exclusion criteria. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axSpA.

Table 1 Patient demographics and other baseline characteristics (full analysis set)

Characteristic	Brodalumab 210 mg N=80	Placebo N=79
Sex, male—n (%)	66 (82.5)	61 (77.2)
Mean age (SD)—years	36.6 (11.4)	38.3 (10.8)
Mean BMI (SD)—kg/m ²	25.1 (4.2)	25.4 (4.1)
Disease subpopulations— n (%)		
AS	63 (78.8)	62 (78.5)
nr-axSpA	17 (21.3)	16 (20.3)
Missing*	0	1 (1.3)
Disease duration of axSpA†—n	75	75
Mean (SD)—years	7.1 (7.7)	6.5 (6.5)
Range—years	0.1–33.9	0.1–26.8
Region—n (%)		
Japan	15 (18.8)	15 (19.0)
Korea	22 (27.5)	22 (27.8)
Taiwan	43 (53.8)	42 (53.2)
Spondyloarthritis features—n (%)		
Inflammatory back pain	79 (98.8)	79 (100.0)
Arthritis	25 (31.3)	35 (44.3)
Enthesitis (heel)	18 (22.5)	19 (24.1)
Uveitis	16 (20.0)	11 (13.9)
Dactylitis	2 (2.5)	4 (5.1)
Psoriasis	6 (7.5)	5 (6.3)
Good response to NSAIDs	25 (31.3)	31 (39.2)
Family history of spondyloarthritis	21 (26.3)	31 (39.2)
HLA-B27 positive	68 (85.0)	65 (82.3)
Elevated CRP‡	49 (61.3)	46 (58.2)
Prior anti-TNF therapy—n (%)	16 (20.0)	17 (21.5)
Adalimumab	4 (5.0)	4 (5.1)
Certolizumab pegol	4 (5.0)	3 (3.8)
Etanercept	6 (7.5)	5 (6.3)
Golimumab	0	2 (2.5)
Infliximab	2 (2.5)	3 (3.8)
Prior anti-IL-12/23 therapy—n (%)	0	0
CRP level at screening, mean (SD)—mg/dL	1.22 (1.45)	1.15 (1.19)
ASDAS-CRP score, mean (SD)	2.660 (0.615)	2.716 (0.652)
BASFI score, mean (SD)	3.7 (2.3)	3.5 (2.5)
BASDAI score, mean (SD)	6.2 (1.4)	6.4 (1.6)
BASMI score, mean (SD)	2.3 (1.7)	2.9 (1.9)

*The patient was initially randomised to the nr-axSpA subgroup at enrolment based on HLA-B-positive results observed on flow cytometry analysis at a local laboratory. However, based on HLA-B-negative results identified later using PCR-SBT at the central lab, the patient was excluded from the nr-axSpA subpopulation.

†Time from diagnosis to study enrolment.

‡CRP above ULN (0.5 mg/dL).

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BMI, body mass index; CRP, C-reactive protein; HLA, human leucocyte antigen; IL, interleukin; nr-axSpA, non-radiographic axSpA; NSAID, non-steroidal anti-inflammatory drug; PCR-SBT, PCR-sequenced based typing; TNF, tumour necrosis factor; ULN, upper limit of normal.

feature (excluding Crohn’s disease) by the ASAS classification criteria for axSpA.¹ In the absence of radiographic evidence for AS, either of the following criteria was required to be met for a diagnosis of nr-axSpA: presence of inflammatory lesions of the sacroiliac joint on magnetic resonance imaging (MRI) of SpA Research Consortium of Canada level ≥ 2 and ≥ 1 SpA feature by the ASAS classification criteria for axSpA (excluding Crohn’s

disease) OR human leucocyte antigen (HLA)-B27 positivity and ≥ 2 SpA features by the ASAS classification criteria for axSpA (excluding Crohn’s disease), with one of these being elevated CRP $>ULN$ (0.5 mg/dL) (online supplemental tables S1 and S2). Radiographic sacroiliitis and inflammatory lesions on MRI were read centrally by a single experienced reader. Other inclusion criteria were Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 (including a spinal pain score ≥ 4) and inadequate response to NSAID therapy of ≥ 3 months. Patients receiving prior therapy were included if the duration of conventional synthetic DMARDs was ≥ 3 months before study drug initiation, with a stable dose for ≥ 4 weeks, or the duration of oral corticosteroids was ≥ 4 weeks before study drug initiation. Patients with complete ankylosis of the spine; history of Crohn’s disease; history/evidence of suicidal ideation (severity: 4 or 5)/any suicidal behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS), or severe depression based on the Patient Health Questionnaire-8 (PHQ-8); or previous biologic therapies, including >1 anti-tumour necrosis factor (anti-TNF) or any anti-TNF within 4–10 weeks of study start or anti-IL-17 or anti-IL-12/IL-23 within 6 months were excluded from the study (online supplemental table S1).

Outcome measures

The primary endpoint was the proportion of patients with axSpA achieving an ASAS 40 response at week 16. Secondary endpoints included the proportion of patients with axSpA achieving ASAS 20, those with AS and nr-axSpA achieving ASAS 40 at week 16, change from baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) using CRP (ASDAS-CRP) at week 16 and ASDAS-CRP response rate by disease improvement and disease activity state. ASAS 20 response rate in the AS subpopulation was assessed post hoc. ASAS 40 response was defined as an improvement of $\geq 40\%$ ($\geq 20\%$ for ASAS 20) and an absolute improvement of ≥ 2 units (≥ 1 unit for ASAS 20) (on a 10-unit scale) in ≥ 3 of the four main ASAS domains (ie, Patient Global Assessment (PGA) of axSpA, the average of total and nocturnal PGA of spinal pain, Bath Ankylosing Spondylitis Functional Index (BASFI) score and the mean of BASDAI Q5 and Q6) and no worsening (by $\geq 20\%$ and ≥ 1 unit for ASAS 20) in the remaining domains.

Treatment-emergent adverse events (TEAEs) were summarised by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (V.19.1). TEAEs identified or considered as potential risks were assessed as ‘TEAEs of interest’ and labelled in the following six categories: neutrophil count decreased/serious infections/serious hypersensitivity (identified risks) and malignancy/inflammatory bowel disease/suicide or self-injury-related events (potential risks) (online supplemental tables S3 and S4).

Exploratory endpoints included BASFI, BASDAI, Bath Ankylosing Spondylitis Metrology Index (BASMI), AS Quality of Life Questionnaire (ASQoL), Short Form-36 (SF-36) Health Survey (version 2), enthesitis count, swollen joint count and PGA of spine pain and axSpA.

Subgroup analyses by prior anti-TNF therapy, HLA-B27 status and CRP level at screening were performed for ASAS 40 response rate at week 16.

Statistical analyses

At least 59 patients per treatment group were targeted for enrolment to achieve a power of 90% with a two-sided 5% significance level assuming an ASAS 40 response rate of 40.5% with

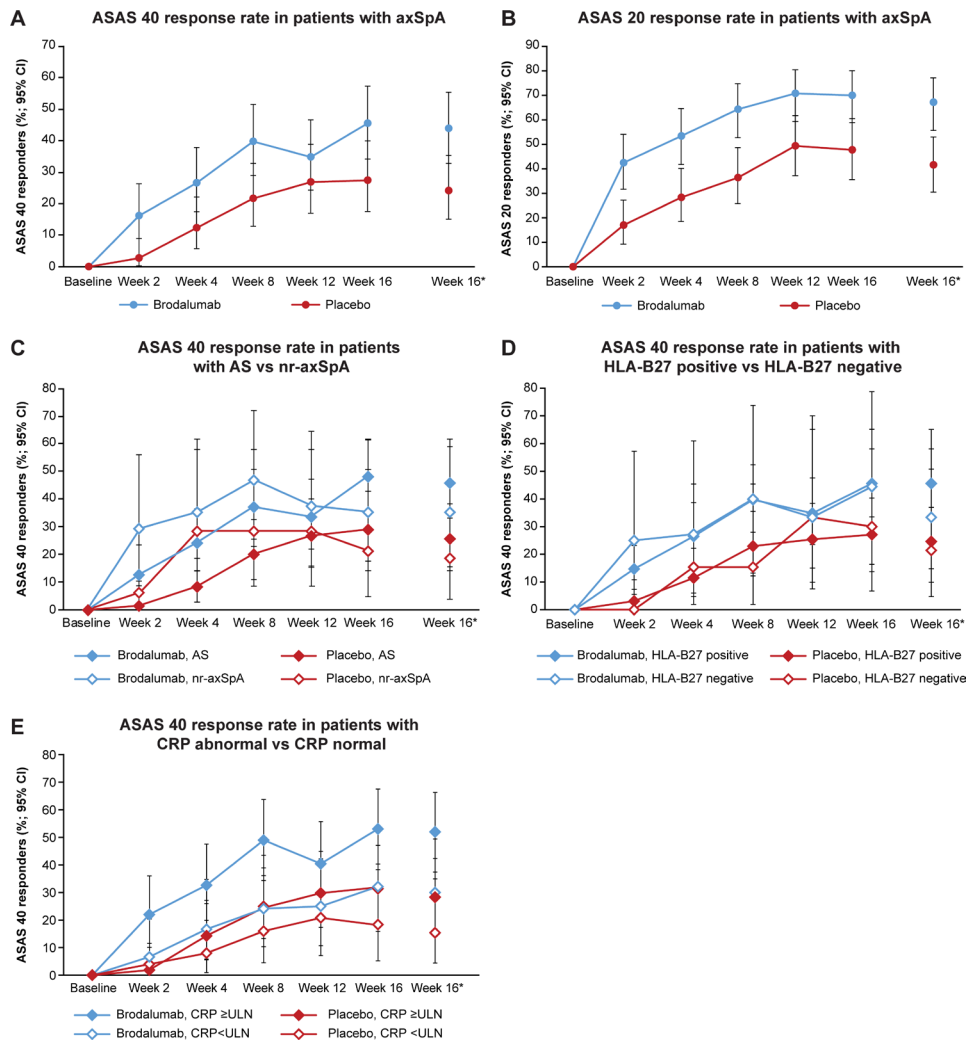


Figure 2 Response rates (full analysis set). (A) ASAS 40 response rate in patients with axSpA. (B) ASAS 20 response rate in patients with axSpA. (C) ASAS 40 response rate in patients with AS vs nr-axSpA. (D) ASAS 40 response rate in patients with HLA-B27 positive vs HLA-B27 negative. (E) ASAS 40 response rate in patients with CRP abnormal vs CRP normal. *Data are presented in online supplemental table S5. AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; axSpA, axial spondyloarthritis; CRP, C-reactive protein; HLA, human leucocyte antigen; nr-axSpA, non-radiographic axSpA; ULN, upper limit of normal.

brodalumab and 13.0% with placebo. The sample size was estimated based on the clinically significant difference in ASAS 40 response rate achieved in AS patients with secukinumab (~40%) and placebo (~12%) in the MEASURE 1 and MEASURE 2 studies¹⁵ and that in nr-axSpA patients with anti-TNF agents (43%) and placebo (15%) in five clinical studies and the expected number of enrolled nr-axSpA patients (maximum possible: 30 patients).⁴ This study was not powered to demonstrate treatment group differences by AS and nr-axSpA.

The full analysis set comprised all randomised patients associated with the assigned treatment excluding those who received no study drug or had no post-dosing efficacy data. The safety analysis set comprised all randomised patients associated with the assigned treatment excluding those who received no study drug.

Missing data at week 16 were imputed as no response for ASAS 20/40 and baseline-observation-carried-forward (BOCF) for ASDAS-CRP. ASAS 40 response rate at week 16 was compared between brodalumab and placebo using the Cochran-Mantel-Haenszel test adjusted with all stratification factors used for randomisation, except IC for PK additional sampling.

For each treatment group, ASAS 20/40 was summarised by visit, and the point estimates and 95% CIs of ASAS 20/40 were calculated. The point estimate and 95% CI of ASDAS-CRP and the change from baseline at week 16 were calculated for each treatment group using an analysis of covariance model adjusted with the baseline ASDAS-CRP and all stratification factors used for randomisation, except IC for PK additional sampling. Data were analysed using SAS V.9.4.

RESULTS

Patients

Overall, 159 eligible patients with axSpA were randomised 1:1 to receive brodalumab 210 mg (n=80) or placebo (n=79; figure 1). Of these, three in the brodalumab group and ten in the placebo group discontinued (figure 1), and 77 and 69, respectively, completed the 16-week period. No patient met the exclusion criteria based on the C-SSRS rating and/or PHQ-8 score.

The study population comprised mainly men (brodalumab: 66 (82.5%); placebo: 61 (77.2%)) and patients with AS (brodalumab: 63 (78.8%); placebo: 62 (78.5%)). The mean age was 36.6 years and 38.3 years in the brodalumab and placebo groups,

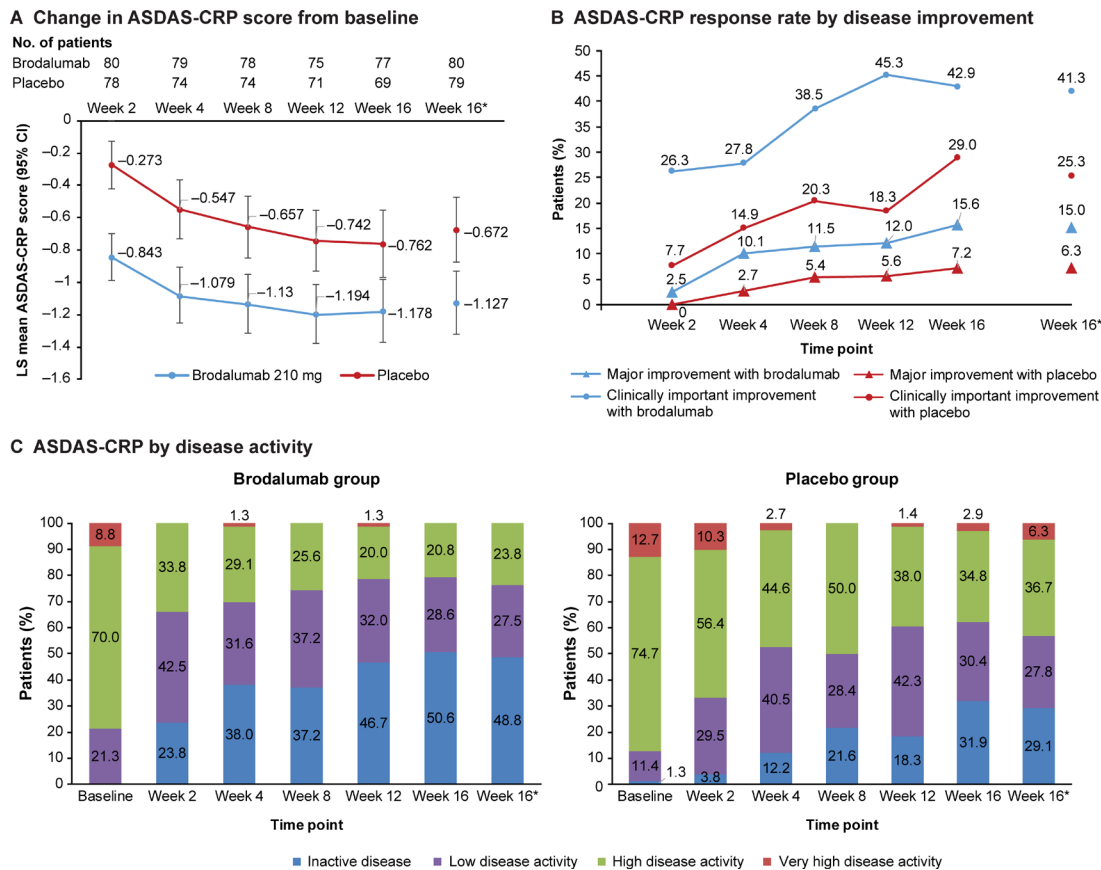


Figure 3 ASDAS-CRP (full analysis set). (A) Change in ASDAS-CRP score from baseline at each efficacy timepoint over 16 weeks. *Baseline-observation-carried-forward ASAS response at week 16. (B) ASDAS-CRP response rate by disease improvement. Disease improvement was defined as clinically important and major for change from baseline in the ASDAS-CRP score of ≥ 1.1 and ≥ 2.0 , respectively. (C) ASDAS-CRP response rate by disease activity state in the brodalumab (left) and placebo (right) groups. Disease activity state was defined by ASDAS-CRP score as follows: score < 1.3 , inactive disease; 1.3 to < 2.1 , low disease activity; 2.1 to < 3.5 , high disease activity; and ≥ 3.5 , very high disease activity. ASAS, Assessment of SpondyloArthritis International Society; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score using C-reactive protein; LS, least squares.

respectively. Approximately 20% of patients in each treatment group had received prior anti-TNF therapy (table 1).

Efficacy

The primary endpoint, ASAS 40 response at week 16 (95% CI; non-responder imputation (NRI)), was achieved in 35 patients with axSpA (43.8%; 32.7, 55.3) in the brodalumab group (rate difference, 19.7% (5.3, 34.1); $p=0.018$) vs 19 patients (24.1%; 15.1, 35.0) in the placebo group (figure 2A and online supplemental table S5). The ASAS 20 response rate (95% CI; NRI) was higher with brodalumab (67.5%; 56.1, 77.6) vs placebo (41.8%; 30.8, 53.4) among patients with axSpA (figure 2B). Among subpopulations with AS and nr-axSpA (figure 2C and online supplemental table S5), the ASAS 40 response rate (95% CI; NRI) at week 16 was higher with brodalumab (AS: 46.0%; 33.4, 59.1, nr-axSpA: 35.3%; 14.2, 61.7) vs placebo (AS: 25.8%; 15.5, 38.5, nr-axSpA: 18.8%; 4.0, 45.6). In the AS subpopulation, the ASAS 20 response rate (n/N; 95% CI; NRI) at week 16 was 69.8% (44/63; 57.0, 80.8) with brodalumab vs 41.9% (26/62; 29.5, 55.2) with placebo. ASAS 40 response rate in the nr-axSpA subpopulation by MRI status is shown in online supplemental table S6.

Among anti-TNF-naïve patients, the ASAS 40 response rate was 45.3% (29/64) with brodalumab vs 25.8% (16/62) with placebo compared with 37.5% (6/16) vs 17.6% (3/17), respectively, for anti-TNF-experienced patients at week 16 (data not

shown). The ASAS 40 response rate at week 16 was higher in patients with HLA-B27 positivity than in those with HLA-B27 negativity (brodalumab, 45.6% (31/68) vs 33.3% (4/12); placebo, 24.6% (16/65) vs 21.4% (3/14); figure 2D and online supplemental table S5) and in those with CRP level \geq ULN vs CRP level $<$ ULN (brodalumab, 52.0% (26/50) vs 30.0% (9/30); placebo, 28.3% (15/53) vs 15.4% (4/26)) (figure 2E and online supplemental table S5).

The least squares mean (LSM) (95% CI; BOCF) change from baseline in ASDAS-CRP was -1.127 ($-1.322, -0.931$) with brodalumab vs -0.672 ($-0.872, -0.473$) with placebo at week 16 (figure 3A), with an LSM difference (95% CI) in the change from baseline in ASDAS-CRP between the two groups of -0.454 ($-0.689, -0.219$). The proportion of patients with major and clinically important improvement at week 16 was 15.0% (12/80) and 41.3% (33/80), respectively, with brodalumab vs 6.3% (5/79) and 25.3% (20/79), respectively, with placebo (figure 3B). At week 16, 48.8% (39/80) of patients had inactive disease and 27.5% (22/80) had low disease activity in the brodalumab group (figure 3C). Improvements from baseline in BASFI, BASDAI, BASMI, enthesitis count, swollen joint count and PGA of spinal pain and axSpA at week 16 were slightly higher with brodalumab than with placebo (online supplemental table S7).

Table 2 Safety summary (safety analysis set)

TEAE—n (%)	Brodalumab 210 mg N=80	Placebo N=79
Any TEAE	44 (55.0)	45 (57.0)
Deaths	0	0
Other serious TEAEs*	4 (5.0)	1 (1.3)
Other significant TEAEs†	4 (5.0)	3 (3.8)
Any drug-related TEAE	26 (32.5)	20 (25.3)
Deaths	0	0
Other serious TEAEs*	1 (1.3)	0
Other significant TEAEs†	2 (2.5)	3 (3.8)
TEAEs of interest‡—n (%)		
Any TEAE	7 (8.8)	2 (2.5)
Inflammatory bowel disease§	4 (5.0)	2 (2.5)
Mouth ulceration	3 (3.8)	1 (1.3)
Stomatitis	1 (1.3)	1 (1.3)
Neutrophil count decreased	1 (1.3)	0
Leucopenia	1 (1.3)	0
Serious infections	2 (2.5)	0
Herpes zoster oticus	1 (1.3)	0
External ear cellulitis	1 (1.3)	0
Suicide/self-injury-related events	0	0
Serious hypersensitivity	0	0
Malignancy	0	0

*Any serious TEAE other than death.

†Any non-serious TEAE leading to withdrawal of the study drug or dose suspension.

‡TEAEs identified or considered as potential risks were assessed as 'TEAEs of interest' and labelled in the following six categories: neutrophil count decreased/serious infections/serious hypersensitivity (identified risks) and malignancy/inflammatory bowel disease/suicide or self-injury-related events (potential risks) (online supplemental tables S3 and S4).

§Ulcerative colitis or Crohn's disease was not reported in any patient. TEAE, treatment-emergent adverse event.

Safety

Over 16 weeks, TEAEs were reported in 44 (55%) patients in the brodalumab group and 45 (57%) patients in the placebo group (table 2). No deaths were reported. The most commonly reported TEAEs by SOC in the brodalumab group were infections and infestations (n=18, 22.5%; placebo: n=15, 19.0%), gastrointestinal disorders (n=13, 16.3%; placebo: n=7, 8.9%) and investigations (n=7, 8.8%; placebo: n=1, 1.3%).

The most commonly reported TEAEs by PT in the brodalumab group were nasopharyngitis (10.0% (n=8); placebo: 11.4% (n=9)) and alanine aminotransferase and aspartate aminotransferase increased (5% (n=4) each; placebo: 1.3% (n=1) each) (table 3). Ulcerative colitis, Crohn's disease, candidiasis or uveitis were not reported in any patient. Of the seven (8.8%) patients in the brodalumab group reporting TEAEs of interest, three had mouth ulceration and one each had stomatitis, herpes zoster oticus, external ear cellulitis and leucopenia. Other serious TEAEs were reported in four (5.0%) patients in the brodalumab group, all of which resolved, and included malocclusion/ankle fracture/external ear cellulitis (all drug unrelated) and herpes zoster oticus (relationship with drug unknown) in one patient each. In the placebo group, one serious TEAE of back pain was reported. No patient reported suicidal ideation or suicidal behaviour.

DISCUSSION

In patients with AS and nr-axSpA, the efficacy and safety of selective IL-17 A and/or F blockade were demonstrated

Table 3 TEAEs by SOC and PT

TEAEs (any TEAE ≥2.5% in any treatment group)—n (%)	Brodalumab 210 mg N=80	Placebo N=79
Infections and infestations	18 (22.5)	15 (19.0)
Nasopharyngitis	8 (10.0)	9 (11.4)
Rhinitis	3 (3.8)	1 (1.3)
Upper respiratory tract infection	2 (2.5)	5 (6.3)
Gastrointestinal disorders	13 (16.3)	7 (8.9)
Diarrhoea	3 (3.8)	1 (1.3)
Mouth ulceration	3 (3.8)	1 (1.3)
Abdominal pain upper	2 (2.5)	0
Vomiting	2 (2.5)	0
Investigations	7 (8.8)	1 (1.3)
Alanine aminotransferase increased	4 (5.0)	1 (1.3)
Aspartate aminotransferase increased	4 (5.0)	1 (1.3)
Liver function test abnormal	2 (2.5)	0
Musculoskeletal and connective tissue disorders	6 (7.5)	6 (7.6)
Back pain	0	2 (2.5)
Injury, poisoning and procedural complications	5 (6.3)	6 (7.6)
Ligament sprain	1 (1.3)	2 (2.5)
Metabolism and nutrition disorders	4 (5.0)	2 (2.5)
Nervous system disorders	3 (3.8)	2 (2.5)
Skin and subcutaneous tissue disorders	3 (3.8)	5 (6.3)
Pruritus	2 (2.5)	1 (1.3)
General disorders and administration site conditions	2 (2.5)	6 (7.6)
Fatigue	1 (1.3)	2 (2.5)
Respiratory, thoracic and mediastinal disorders	2 (2.5)	3 (3.8)
Vascular disorders	2 (2.5)	2 (2.5)
Hypertension	2 (2.5)	2 (2.5)

PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

previously.^{13–24} However, this is the first study in patients with axSpA comprising subpopulations of both disease subtypes, AS and nr-axSpA, which reports the efficacy and safety of brodalumab, an IL-17RA monoclonal antibody that inhibits multiple IL-17 cytokines.²⁷ Over 16 weeks, the ASAS 40 response rate in patients with axSpA consistently improved with brodalumab and was significantly higher vs placebo at week 16.

ASAS 40/20 responses were observed as early as week 2 among patients treated with brodalumab; at week 16, 43.8%/67.5% of patients demonstrated ASAS 40/20 response. The ASAS 40 response rate with brodalumab at week 16 was comparable in the subpopulations with AS (46.0%) and nr-axSpA (35.3%). Disease activity (as assessed by the ASDAS-CRP score) started improving as early as week 2 and consistently improved over 16 weeks. At week 16, 76.3% of patients achieved inactive disease or low disease activity, and 41.3% of patients had major and/or clinically important improvement with brodalumab treatment. The incidence of TEAEs was similar between the placebo and brodalumab groups, with no new safety signals identified with brodalumab treatment over 16 weeks. Importantly, no TEAEs related to suicidal ideation or behaviour were reported, as cautioned in the brodalumab label.³¹

The ASAS 40/20 response rates observed in this study with brodalumab in patients with AS (46.0%/69.8%) were comparable with those achieved at week 16 with secukinumab in previous studies in Asian (43.5%/69.6%)¹⁷ and Japanese

(46.7%/70.0%)¹⁹ populations with active AS. The improvement in ASDAS-CRP was also similar to that previously reported with secukinumab in the Asian population.¹⁷ Although the study populations were similar, comparison between studies should be undertaken with caution because the efficacy may be impacted by other patient characteristics, such as CRP levels and HLA-B27 positivity. ASAS 40/20 response rates of 38.8%/59.5% and 35.9%/61.5% at week 16 with secukinumab with and without a loading dose, respectively,¹⁸ and 30%–46%/41%–72% at week 12 with 16–320 mg doses of bimekizumab have been reported previously in global populations.²⁰

In patients with nr-axSpA, the ASAS 40 response rate achieved at week 16 in the current study (35.3%) was comparable to that achieved in the global COAST-X study (35%–40%) at week 16 with ixekizumab, an IL-17A inhibitor.²⁴

The global phase 3 studies, COAST-V in biological DMARD-naïve²¹ and COAST-W in anti-TNF-experienced patients¹³ with AS, reported ASAS 40 response rates at 16 weeks of about 50% and 25%–30%, respectively, with two dose regimens of ixekizumab. Subgroup analyses in our study demonstrated comparable ASAS 40 response rates in anti-TNF-naïve (45.3%) and anti-TNF-experienced (37.5%) patients with brodalumab. The results from the global phase 3 study of secukinumab also suggested that prior anti-TNF use may not impact response with IL-17 inhibitors.¹⁸ High CRP levels and HLA-B27 positivity were previously reported as good predictors of response in patients with SpA/AS treated with anti-TNF agents.^{32–34} In this study as well, HLA-B27 positivity (vs negativity) and CRP levels \geq ULN (vs $<$ ULN) were associated with higher ASAS 40 response rates in brodalumab-treated patients.

Improvement in BASDAI at week 16 (mean, -2.9) was comparable to that (LSM, -2.6) previously reported with secukinumab in the Asian population.¹⁷ Improvement in other measures, including patient-reported outcomes (PROs), in the present study was negligible vs placebo and lower for ASQoL and SF-36. A similar high placebo effect on subjective PROs was reported with secukinumab at 2 years in a global population¹⁸ and was attributed to the growing awareness about the efficacy of this drug. However, the relatively long disease duration (7.1 years) of the brodalumab group could also be a reason, where causes other than inflammation (such as non-physiological stress, chronic muscle imbalance) potentially contributed more to disease symptoms, leading to a disconnect between improvement in objective and subjective signs, as reported previously.³⁵ The safety profile of brodalumab in the current study was similar to that reported in previous global and Japanese studies of psoriasis.^{36,37}

Study limitations include limited generalisability of results since the study population was specific to Japan, Korea and Taiwan, where Kyowa Kirin has development/marketing rights; inability to assess statistical significance between disease subpopulations due to the small sample size of the nr-axSpA population; and unavailability of MRI outcomes until 16 weeks. Further, the number of patients with AS exceeded the planned sample size of 90 because too many patients were screened due to the concern of not being able to reach the targeted sample size, arising from a high rate of screening failures initially. Moreover, the current results demonstrate the short-term efficacy and safety of brodalumab treatment in axSpA. The 52-week (weeks 16–68) results from the open-label extension of this study will further confirm the long-term efficacy and safety of brodalumab.

In conclusion, this study demonstrated that brodalumab is a potential therapeutic option for patients with axSpA.

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