Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and -2 trials

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SUPPLEMENTARY INFORMATION

Number of investigational sites and patients per country

AMVISION 1

Country	Number of sites	Number of patients
Belgium	1	2
Bulgaria	4	9
Canada	4	9
Czech Republic	7	19
Estonia	2	9
France	6	8
Greece	4	6
Hungary	6	15
Italy	4	9
Mexico	5	12
Poland	16	139
Russian Federation	9	71
Slovakia	4	15
Spain	6	21
Switzerland	4	12
United Kingdom	5	15
United States	33	107

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AMVISION-2

Country	Number of sites	Number of patients
Canada	7	32
France	5	11
Germany	4	27
Greece	5	11
Hungary	5	20
Latvia	3	15
Mexico	3	13
Poland	18	177
Russian Federation	10	56
United States	28	122

SUPPLEMENTARY METHODS

Full inclusion and exclusion criteria. Text in bold depicts the changes implemented after the protocol amendment.

Inclusion criteria

- Informed consent prior to initiation of any trial-specific activities/procedures
- ≥18 years of age at time of screening
- Diagnosis of psoriatic arthritis (PsA) for at least 6 months and currently meets the ClASsification for Psoriatic ARthritis (CASPAR) criteria
- ≥3 tender and ≥3 swollen joints (excluding the distal interphalangeal joints as part of a 66/68 joint count) at screening and at baseline
- At least one erosion of the hands or feet (centrally read) or C-reactive protein (CRP) ≥1.0 mg/dL

- An active psoriatic skin lesion (at least one psoriatic plaque approximately 2 cm or more in diameter)
- History of intolerance or inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) and/or disease-modifying antirheumatic drugs (DMARDs) for PsA
- For subjects receiving NSAIDs (including as needed use): the subject must be on a stable dose for ≥4 weeks prior to initiation of investigational product
- For subjects receiving methotrexate, sulfasalazine or leflunomide: subject has received treatment for ≥3 months, with a stable dose (not to exceed 25 mg methotrexate per week, 3 g sulfasalazine per day or 20 mg leflunomide per day) for ≥4 weeks prior to initiation of investigational product
- For subjects receiving oral corticosteroids: the subject must be on a stable dose (not to exceed the equivalent of 10 mg of prednisone per day) for ≥4 weeks prior to initiation of investigational product

Exclusion criteria

- Other medical conditions
    - Known history of active tuberculosis (TB; positive test for tuberculosis during screening defined as either positive purified protein derivative (≥ 5 mm of induration at 48 to 72 hours after test is placed) OR positive Quantiferon test)
    - Subjects with a positive purified protein derivative (PPD) and a history of bacillus Calmette–Guérin vaccination are allowed with a negative Quantiferon test

- Subjects with a positive PPD test (without a history of bacillus Calmette–Guérin vaccination) or subjects with a positive or indeterminate Quantiferon test are allowed if they have all of the following:
  - No symptoms per TB worksheet
  - Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB) per local standard of care prior to the start of investigational product
  - No known exposure to a case of active TB after most recent prophylaxis
  - No evidence of active TB on chest radiograph within 3 months prior to the first dose of investigational product
- Planned surgical intervention between baseline and the Week 52 evaluation
- Active infection or history of infections as follows:
  - Any active infection for which systemic anti-infectives were used within 28 days prior to first investigational product dose
  - A serious infection, defined as requiring hospitalisation or intravenous anti-infectives within 8 weeks prior to the first investigational product dose
  - Recurrent or chronic infections or other active infection that, in the opinion of the investigator, might cause this trial to be detrimental to the subject
- Any systemic disease (eg, renal failure, heart failure, hypertension, liver disease, diabetes, anaemia) considered by the investigator to be clinically significant and uncontrolled.

- Known history of human immunodeficiency virus 207.
- Positive hepatitis B surface antigen, hepatitis B core antibody or hepatitis C virus antibody serology.
- Myocardial infarction, unstable angina pectoris or stroke within the past 12 months prior to the first investigational product dose.
- Any active malignancy, including evidence of cutaneous basal or squamous cell carcinoma or melanoma.
- History of malignancy within the last 5 years EXCEPT treated and considered cured cutaneous basal or squamous cell carcinoma, *in situ* cervical cancer or *in situ* breast ductal carcinoma.
- Any concurrent medical condition or electrocardiogram (ECG) abnormality that, in the opinion of the investigator, could cause this trial to be detrimental to the subject.
- Active Crohn's disease or a history of Crohn's disease.

- Laboratory abnormalities
  - Any of the following laboratory abnormalities at screening:
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 × the upper limit of normal (ULN)
    - Serum direct bilirubin ≥1.5 mg/dL (25.7 μmol/L)
    - White blood cell (WBC) count $<3.00 \times 10^3/\mu L$
    - Absolute neutrophil count (ANC) $<2.00 \times 10^3/\mu L$
    - Subject has any other laboratory abnormality, which, in the opinion of the investigator, will prevent the subject from completing the trial or will interfere with the interpretation of the trial results

- Washouts or other treatments

- Use of any of the following within 28 days of investigational product initiation: hydroxychloroquine, cyclosporine, systemically administered calcineurin inhibitors, azathioprine, parenteral corticosteroids including intramuscular or intraarticular administration, live vaccines
- Use of a narcotic analgesic within 24 hours prior to the baseline visit
- Use of a topical therapy as follows:
    - Super-potent or potent topical steroids or topical anthralin/dithranol within 28 days before first dose of investigational product
    - Any other formulation or potency of topical therapy within 14 days before first dose of investigational product (exception: upper mid-strength or lower potency topical steroids permitted on the face, axillae, and groin); bland emollients (without urea or alpha or beta hydroxy acids); shampoo without steroids
- Use of the following within 28 days of first dose of investigational product: ultraviolet A light therapy (with or without psoralen); ultraviolet B light therapy; excimer laser; oral retinoids; Tioguanine; Hydroxycarbamide (Hydroxyurea); fumarates for psoriasis; other non-biologic systemic therapy for psoriasis.
- Use of commercially available or investigational biologic therapies for psoriasis and/or PsA as follows:
    - Anti-tumour necrosis factor (anti-TNF) therapy within 2 months prior to investigational product initiation
    - Other experimental or commercially available biologic therapies for psoriasis and/or PsA within 3 months prior to investigational product initiation

  - Anti-IL17 or anti-IL12/IL23 biologic therapy, including brodalumab, secukinumab, ixekizumab, ustekinumab, briakinumab at any time
  - Rituximab at any time

- General
  - Currently receiving treatment in another investigational device or drug trial, or less than 30 days since ending treatment on another investigational device or drug trial(s) prior to screening.
  - Other investigational procedures while participating in this trial are excluded.
  - Known sensitivity to any of the products or components to be administered during dosing.
  - Subject likely to not be available to complete all protocol-required trial visits or procedures, and/or to comply with all required trial procedures through Week 24 [eg, Patient-Reported Outcomes (PROs)] to the best of the subject and investigator's knowledge.
  - **History or evidence of suicidal ideation (severity of 4 or 5) or any suicidal behaviour based on an assessment with the Columbia Suicide Severity Rating Scale at screening or at baseline.**
  - History **or evidence of a psychiatric disorder or** substance abuse that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the trial evaluation, procedures or completion.
  - **Severe depression based on a total score of ≥15 on the Patient Health Questionnaire-8 (PHQ-8) at screening or baseline. (note: subjects with**

a total score of 10–14 on the PHQ-8 should referred to a mental health professional).

- History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or physician, if consulted, would pose a risk to subject safety or interfere with the trial evaluation, procedures or completion.
- Subject previously has entered this trial.
- Women who are pregnant or planning to become pregnant while on trial through 8 weeks after the last dose of trial drug.
- Women with a positive pregnancy test (assessed by a serum pregnancy test during screening and a urine pregnancy test at baseline) women who have had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy or are at least 2 years postmenopausal, with postmenopausal status confirmed by follicle-stimulating hormone in the postmenopausal range are not required to have pregnancy tests.
- Women of reproductive potential who are not willing to use an acceptable form of birth control during the trial and for an additional 8 weeks after the last dose of trial drug.
- Women who are lactating/breastfeeding or planning to breastfeed during the trial and for an additional 8 weeks after the last dose of trial drug.

Criteria for permanent discontinuation of investigational product

- Non-response, defined as patients who did not achieve ≥10% improvement from baseline in their tender and swollen joint counts at any visit from Week 28 through Week 34 despite ≥12 weeks of continuous treatment after meeting the criteria for inadequate response

- Suicidal ideation (severity 4 or 5) or any suicidal behaviour after randomisation based on an assessment with the electronic self-rated Columbia Suicide Severity Rating Scale (eC-SSRS)
- Severe depression after randomisation, defined as a total score of ≥ 15 based on an assessment with the Patient Health Questionnaire depression scale (PHQ-8)
- Safety concerns such as:
    - ANC abnormalities
        - Sustained episodes of neutropenia (defined as ANC < 1.00 × 10^3/μL) at all measurements (must be at least 2) for ≥ 4 weeks
        - Second episode of neutropenia (ANC < 1.00 × 103/μL), following full recovery (ANC ≥ 1.00 × 10^3/μL)
        - ANC is < 0.50 × 10^3/μL
    - Hepatotoxicity [drug-induced liver injury (defined as total bilirubin >2 × ULN or international normalised ratio >1.5 AND increased aspartate transaminase or alanine aminotransferase >3 × ULN) AND no other cause for the combination of the laboratory abnormalities is immediately apparent]
- Withdrawal of consent
- Sponsor decision (other than patient request, safety concern)
- Death
- Lost to follow-up

Information on inadequate response

If the criteria for inadequate response were met, initiation and/or dose adjustments of the non-biologic DMARDs methotrexate, sulfasalazine or leflunomide were allowed. For patients who were already receiving these treatments, upward dose titration per

local standard of care was allowed; however, methotrexate and leflunomide could not be used concurrently. In addition, initiation and/or dose adjustments of oral corticosteroids and NSAIDs were allowed to supplement treatment with non-biologic DMARDs. Patients on placebo with inadequate response were switched to brodalumab 210 mg. From Week 24, patients who were originally randomised to placebo and had not already met criteria for inadequate response received brodalumab 210 mg with an additional dose at Week 25. Patients who were originally randomised to one of the brodalumab treatments remained on the same Q2W dose with an additional dose of placebo at Week 25 to maintain the blind.

Definitions of trial endpoints

ACR 20

A positive ACR 20 response is defined as at least 20% improvement from baseline in both tender/painful (68 joints) and swollen joint counts (66 joints), and a 20% or more improvement in at least three of the following five criteria: physician global assessment of arthritis disease activity (PhGA, 0–100 visual analogue scale), patient global assessment of arthritis disease activity (PtGA, 0–100 visual analogue scale), patient global assessment of joint pain (0–100 visual analogue scale), HAQ-DI, and acute phase reactant: erythrocyte sedimentation rate (ESR) or CRP, whichever has greater improvement.[1]

ACR 50

A positive ACR 50 response is defined by using the definition of ACR20 response described above but requiring at least 50% improvement.

ACR 70

A positive ACR 70 response is defined by using the definition of ACR20 response described above but requiring at least 70% improvement.

Clinical Disease Activity Index (CDAI)

CDAI is a composite score that is based on a 28-joint count (using 28 tender/painful and 28 swollen joints, the 28 joint counts include 10 proximal interphalangeal, 10 metacarpophalangeal, 2 wrist, 2 elbow, 2 shoulder, and two knee joints), PhGA (0–100 visual analogue scale), and PtGA (0–100 visual analogue scale).

The scoring algorithm for CDAI is shown below.

CDAI = SW28 + T/P28 + PhGA/10 + PtGA/10

Dactylitis count

The dactylitis count is defined as the sum of 20 fingers/toes that exhibit dactylitis (absent 0, present 1).

Disease activity in psoriatic arthritis (DAPSA)

DAPSA was a post hoc analysis and is a joint-specific composite measure of disease activity calculated by summing swollen + tender joint counts + patient pain + patient global assessments + CRP, using 66/68 joint counts, as defined below.

DAPSA = TJC + SJC + patient assessed disease activity/10 + patient assessed pain/10 + CRP (mg/dL)

DAS 28 CRP

The DAS 28 CRP is a composite score that is based on a 28-joint count (using 28 tender/painful and 28 swollen joints), CRP and PtGA. The 28 joint counts include 10 proximal interphalangeal, 10 metacarpophalangeal, 2 wrist, 2 elbow, 2 shoulder and 2 knee joints. The scoring algorithm for the DAS28CRP is shown below.

DAS28CRP = $0.56 \sqrt{T/P28} + 0.28 \sqrt{SW28} + 0.36 \times \ln(CRP + 1) + 0.014 \times PtGA + 0.96$.

Enthesitis count

The enthesitis count is defined as the total number of six sites that have enthesitis. The sites to be assessed are: lateral epicondyle (left/right), medial femoral condyle (left/right), Achilles' tendon insertion (left/right).

HAQ-DI score

The HAQ-DI is defined as the average of the scores from eight sub-domains (dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities). HAQ-DI scores range from 0 (no difficulty) to 3 (much difficulty) for each of the 20 questions in the eight categories.

The maximum score for each of the eight categories should be calculated (7 of the categories are listed in the table below. The eighth category 'Activities' is not listed in the table due to lack of questions regarding use of aids or device). At least one question in each category needs to be answered to compute the maximum score. If an aid or device is used or help from another person is needed, adjust the score for the associated category by increasing a zero or a one to a two. If a patient's highest score for that category is a 2, it remains a 2, and if a 3, it remains a 3.

Sub-domain	**Aids or devices**
Dressing and grooming	Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
Arising	Special or built up chair
Eating	Built up or special utensils
Walking	Cane, walker, crutches, wheelchair
Hygiene	Raised toilet seat, bathtub seat, bathtub bar, long-handled appliances in bathroom
Reach	Long-handled appliances for reach
Grip	Jar opener (for jars previously opened)

If no more than two categories have missing scores, then the disability score is the mean of the non-missing category scores. Otherwise, the disability score is set to missing.

Psoriatic Arthritis Disease Activity Score

The PASDAS consists of the following domains: physician and patient global assessment of arthritis and skin, peripheral joint counts, dactylitis, enthesitis, CRP and SF-36 v2 physical component summary.

$$PASDAS = (((0.18\sqrt{physician\_global\_assessment\_PsA}) + (0.159\sqrt{patient\_global\_assessment\_PsA}) - (0.253\times\sqrt{SF36-PCS}) + (0.101\times\ln(Swollen\_joint\_count+1)) + (0.048\times\ln(Tender\_joint\_count+1)) + (0.23\times\ln(Leeds\_enthesitis\_count+1)) + (0.37\ln(Tender\_dactylitis\_count+1)) + (0.102\times\ln(CRP+1)) + 2)\times 1.5$$

Note: CRP unit is mg/L.

Supplementary statistical analysis

The AMVISION-1 and -2 studies were designed to detect significant treatment differences in ACR20 response between the brodalumab and placebo arms at Week 16, with >90% power, assuming the underlying rate of response was 45% and 18% in the brodalumab and placebo arms respectively. The additional sample size in AMVISION-1 provided >90% and >80% adjusted power to detect treatment difference in the change from baseline at Week 24 in radiographic progression of joint damage between the brodalumab and placebo arms (radiographic data not shown here). The familywise error rates for the studies were controlled at the 5% level, through the specification of hierarchical testing procedures.

Both studies were terminated by the sponsor (Amgen) prior to reaching their recruitment targets. While the power of the primary endpoint in both studies was reduced but still sufficient, maintaining an adjusted power of >90%, the primary analysis, based on the Cochran–Mantel–Haenszel test was no longer feasible. To account for all randomised patients, this analysis required the use of non-responder

imputation (NRI) to address missing data. However, it was judged inappropriate to treat subjects who were not provided the opportunity to complete the trial as non-responders. To address the issue, a generalised estimating equation (GEE) model, with a logit link function, unstructured working correlation matrix and with visit, prior biologic use, geographical region, baseline body weight and treatment by visit interaction terms included as fixed effects was proposed. For pooled analyses, an additional fixed-term effect was included in the models in order to account for potential differences between studies. For this analysis, patients qualifying for rescue treatment or withdrawing from the trial for any reason other than trial termination were treated as non-responders. Under the assumption that missing data were missing completely at random, the estimated treatment effect obtained from the GEE model is unbiased.

For the analysis of continuous endpoints, the change from baseline was analysed based upon fitting a mixed model for repeated measurements (MMRM). The variance–covariance matrix was assumed to have an unstructured form and the Kenward–Roger approximation was used to estimate the denominator degree of freedoms and adjust the standard errors. The model included the baseline value as a continuous covariate, visit, weight, geographical region and prior biologic use as factor variables and interaction terms between visit and treatment.

Information on early trial termination

The studies were terminated early (24 June 2015) due to a decision by Amgen to stop their participation in the co-development of brodalumab in psoriasis and psoriatic arthritis.. This was based on events of suicidal ideation and behaviour observed in the clinical programme and an anticipation that it would lead to restrictive labelling (see also AstraZeneca press release of 22 May 2015. Available from: https://www.astrazeneca.com/media-centre/press-releases/2015/astrazeneca-brodalumab-development-programme-psoriasis-arthritis-22052015.html#!) (accessed July 2020). The programme was subsequently transitioned to co-developing partner AstraZeneca. Through a collaboration agreement, AstraZeneca granted Valeant (now Bausch Health Companies) the exclusive licence to develop and commercialise brodalumab globally, except in Japan and certain other Asian countries where rights are held by Kyowa Hakko Kirin Co., Ltd (now Kyowa Kirin Co.) through an agreement with Amgen, and in Europe, where LEO Pharma holds exclusive rights to develop and commercialise brodalumab through an agreement entered in July 2016.

SUPPLEMENTARY EFFICACY DATA

Supplementary Table 1 Patient n/N1 numbers for efficacy parameters

Number of patients, n/N1	**AMVISION-1**			**AMVISION-2**			**Pooled**		
Week 16									
	PBO (N=161)	**BRO 140 mg Q2W (N=158)**	**BRO 210 mg Q2W (N=159)**	**PBO (N=161)**	**BRO 140 mg Q2W (N=160)**	**BRO 210 mg Q2W (N=163)**	**PBO (N=322)**	**BRO 140 mg Q2W (N=318)**	**BRO 210 mg Q2W (N=322)**
ACR20	17/95	47/102	63/111	36/133	69/130	61/129	53/228	116/232	124/240
ACR50	5/97	24/102	36/114	13/136	39/131	33/131	18/233	63/233	69/245
ACR70	3/98	12/108	18/116	5/137	18/131	15/134	8/235	30/239	33/250
	PBO (N=103)	**BRO 140 mg Q2W (N=113)**	**BRO 210 mg Q2W (N=102)**	**PBO (N=118)**	**BRO 140 mg Q2W (N=107)**	**BRO 210 mg Q2W (N=117)**	**PBO (N=221)**	**BRO 140 mg Q2W (N=220)**	**BRO 210 mg Q2W (N=219)**
PASI75	8/75	44/85	58/73	11/107	46/89	69/102	19/182	90/174	127/175
PASI90	6/75	36/85	50/73	6/107	32/89	49/102	12/182	68/174	99/175
PASI100	3/75	18/85	37/73	4/107	18/89	36/102	7/182	36/174	73/175
	PBO (N=161)	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**	**PBO (N=161)**	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**	**PBO (N=322)**	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**

		(N=158)	**(N=159)**		**(N=160)**	**(N=163)**		**(N=318)**	**(N=322)**
Dactylitis resolution	11/51	20/56	30/61	28/60	25/49	37/67	31/119	45/105	67/128
Enthesitis resolution	16/72	24/67	25/61	26/87	35/74	34/85	42/159	59/141	59/146
HAQ-DI LS mean change from baseline, n[a]	93	98	107	134	132	127	227	230	234
Achievement of HAQ-DI MCID	27/111	50/108	69/112	47/134	63/120	66/127	74/245	113/228	135/239
DAS28 CRP LS mean change from baseline[a]	93	98	105	133	131	126	226	229	231
CDAI LS mean change from baseline, n[a]	92	98	106	132	128	127	224	226	233
DAPSA LS mean change from baseline [a]	93	98	105	133	131	126	226	229	231
PASDAS LS mean change from	91	98	103	128	128	126	219	226	229

baseline, n[a]

Week 24									
	PBO (N=161)	**BRO 140 mg Q2W (N=158)**	**BRO 210 mg Q2W (N=159)**	**PBO (N=161)**	**BRO 140 mg Q2W (N=160)**	**BRO 210 mg Q2W (N=163)**	**PBO (N=322)**	**BRO 140 mg Q2W (N=318)**	**BRO 210 mg Q2W (N=322)**
ACR20	17/82	51/80	54/85	31/110	52/105	57/99	48/192	103/185	111/184
ACR50	8/82	29/79	36/85	14/110	35/112	42/100	22/192	64/191	78/185
ACR70	3/84	13/82	22/88	7/112	18/113	24/101	10/196	31/195	46/189
	PBO (N=103)	**BRO 140 mg Q2W (N=113)**	**BRO 210 mg Q2W (N=102)**	**PBO (N=118)**	**BRO 140 mg Q2W (N=107)**	**BRO 210 mg Q2W (N=117)**	**PBO (N=221)**	**BRO 140 mg Q2W (N=220)**	**BRO 210 mg Q2W (N=219)**
PASI75	5/65	36/73	47/60	10/90	34/73	54/83	15/155	70/146	101/143
PASI90	2/65	29/73	36/60	4/90	24/73	45/83	6/155	53/146	81/143
PASI100	2/65	18/73	33/60	1/90	18/73	39/83	3/155	36/146	72/143
	PBO (N=161)	**BRO 140 mg Q2W (N=158)**	**BRO 210 mg Q2W (N=159)**	**PBO (N=161)**	**BRO 140 mg Q2W (N=160)**	**BRO 210 mg Q2W (N=163)**	**PBO (N=322)**	**BRO 140 mg Q2W (N=318)**	**BRO 210 mg Q2W (N=322)**
Dactylitis resolution	6/39	15/51	27/49	15/59	23/40	32/53	21/98	38/91	59/102
Enthesitis resolution	12/57	21/60	23/45	20/69	28/60	26/66	32/126	49/120	49/111

HAQ-DI LS mean change from baseline, n[a]	38	71	72	64	83	84	102	154	156
Achievement of HAQ-DI MID	19/88	41/93	54/85	31/106	46/97	51/105	50/194	87/190	105/190
DAS28 CRP LS mean change from baseline, n[a]	37	70	72	62	83	82	99	153	154
CDAI LS mean change from baseline, n[a]	37	70	71	62	82	83	99	152	154
DAPSA LS mean change from baseline, n[a]	37	70	72	62	83	82	99	153	154
PASDAS LS mean change from baseline, n[a]	37	69	71	60	80	81	97	149	152

N, number of patients in treatment group; N1, number of patients with observed data at visit; n, number of patients; n[a], number of patients with baseline and post-baseline results.

ACR, American College of Rheumatology; BRO, brodalumab; CDAI, Clinical Disease Activity Index score; CRP, C-reactive protein; DAPSA, disease activity in psoriatic arthritis; DAS28, disease activity score with a 28-joint count; HAQ-DI, Health Assessment Questionnaire-Disability Index; MID, minimally important difference; PASDAS, psoriatic arthritis disease activity score; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q2W, every 2 weeks.

Supplementary Table 2 Sensitivity analyses for ACR20 responder rates at Week 24

Analysis	**Statistical method**	**Analysis set**	**Trt. comparison**	**Trt. diff. (%)[e]**	**95% CI (%)**
Primary	GEE	FAS[a]	BRO 140 vs PBO	27.2	(19.0, 35.3)
			BRO 210 vs PBO	29.8	(21.6,37.9)
Sensitivity analysis I[f]	CMH	PAS24[b]	BRO 140 vs PBO	26.9	(18.1, 35.6)
			BRO 210 vs PBO	30.9	(22.2, 39.6)
Sensitivity analysis II[g]	GEE	FAS	BRO 140 vs PBO	17.4	(11.0, 23.8)
			BRO 210 vs PBO	19.4	(12.9, 25.9)
	CMH	FAS	BRO 140 vs PBO	17.5	(11.0, 23.9)
			BRO 210 vs PBO	19.6	(13.1, 26.1)
Sensitivity analysis III[h]	GEE	FAS	BRO 140 vs PBO	27.1	(19.0, 35.2)
			BRO 210 vs PBO	30.0	(21.8, 38.1)
Sensitivity analysis IV[i]	MI-GEE[c]	FAS	BRO 140 vs PBO	27.9	(19.4, 36.4)
			BRO 210 vs PBO	30.0	(21.8, 38.4)
Sensitivity analysis V[j]	MI-CMH[d]	FAS	BRO 140 vs PBO	27.7	(19.2, 36.2)
			BRO 210 vs PBO	29.9	(21.6, 38.1)

[a]Consisting of all patients randomised into AMVISION-1 and -2 trials.

[b]Consisting of all patients randomised into the trial whose Week 24 visit was scheduled to occur prior to the decision to terminate the brodalumab development programme.

[c]This approach imputed missing data due to early withdrawal based on NRI. Otherwise, missing data were imputed assuming MAR within treatment arm. The analysis consisted of imputing 500 complete data sets and analysing the complete data sets based on the GEE analysis specified in the primary analysis. Inference was carried out using Rubin's rules. This method should provide valid inferences under the assumption that missing data are MAR.

[d]The same imputation approach was used, as for the MI-GEE analysis. Inference was based on using Rubin's rules to synthesise the estimates of the risk difference based on the CMH test. This method should provide valid inferences under the assumption that missing data is MAR.

[e]Trt. diff: The estimated difference in ACR20 response rates at Week 24 between the treatment arms.

[f]Sensitivity analysis I uses the standard analysis method, the Cochran–Mantel–Haenszel test, to derive the estimated difference in ACR20 response rates at Week 24, based on the Week 24 primary analysis set.

[g]Sensitivity analysis II uses NRI for all missing data, irrespective of the reason for missing data. The GEE model corresponds to the model in the primary analysis. This analysis based on the CMH test is the one specified in the original statistical analysis plan.

[h]Sensitivity analysis III uses NRI to impute missing data due to early withdrawal or intermittent missing data.

[i]Sensitivity analysis IV is described above under the footnote for MI-GEE.

[j]Sensitivity analysis V is described above under the footnote for MI-CMH.

CMH, Cochran–Mantel–Haenszel test; FAS, Full analysis set; GEE, generalised estimating equation; MI-CMH, Multiple imputation – Cochran–Mantel–Haenszel test; MI-GEE, Multiple imputation – Generalised estimating equation; PAS24, Primary analysis set Week 24.

SUPPLEMENTARY SAFETY DATA

Supplementary Table 3 Summary of safety: adverse events up to Week 24 (safety population, pooled analysis)

Adverse events, n (rate per 100 subject years)	**PBO (subject year=107.8)**	**BRO 140 mg Q2W (subject year=121.7)**	**BRO 210 mg Q2W (subject year=123.9)**
All AE[a]	515 (477.6)	476 (391.1)	474 (382.6)
AEs causally related to treatment[b]	127 (117.8)	106 (87.1)	81 (65.4)
SAE	14 (13.0)	9 (7.4)	13 (10.5)
Death	0	0	0
AEs leading to treatment discontinuation	6 (5.6)	6 (4.9)	3 (2.4)
AEs leading to treatment interruption	68 (63.1)	58 (47.7)	54 (43.6)
Selected AEs of interest[c]			
Infections and infestations	157 (145.6)	123 (101.1)	149 (120.3)
Crohn's disease	0	0	0
Neutropenia	0	7 (5.8)	5 (4.0)
Suicidal ideation and behaviour	0	1 (0.8)[d]	0
MACE	2 (1.9)	0	1 (0.8)
Hypersensitivity[e]	2 (1.9)	1 (0.8)	10 (8.1)
Malignancy	0	1 (0.8)	3 (2.4)

[a]All adverse events reported by each subject are included.

[b]Causally related to treatment as assessed by investigator.

[c]Adverse events of interest are important identified risks (eg, infections, neutropenia, worsening of Crohn's disease), important potential risks (eg, hypersensitivity, suicidal behaviour (including attempted/completed suicide attempt), suicidal ideation, MACE, Malignancy) and other events of interest (injection site reactions) in response to the emerging safety profile of brodalumab.

[d]Patient (35 year, F, history of suicidal ideation) diagnosed following the first completed electronic Columbia Suicide Severity Scale assessment, 8 days after first dose; resolved on same day.

[e]Adverse events occurring within one day of an injection and corresponding to the broad scope for the hypersensitivity SMQ have been included.

AE, adverse event; BRO, brodalumab; MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; Q2W, every 2 weeks; SAE, serious adverse event; SMQ, standardised MedDRA query.

Supplementary Table 4 Comparison of brodalumab vs placebo at Week 16, NRI (Primary Analysis Set)

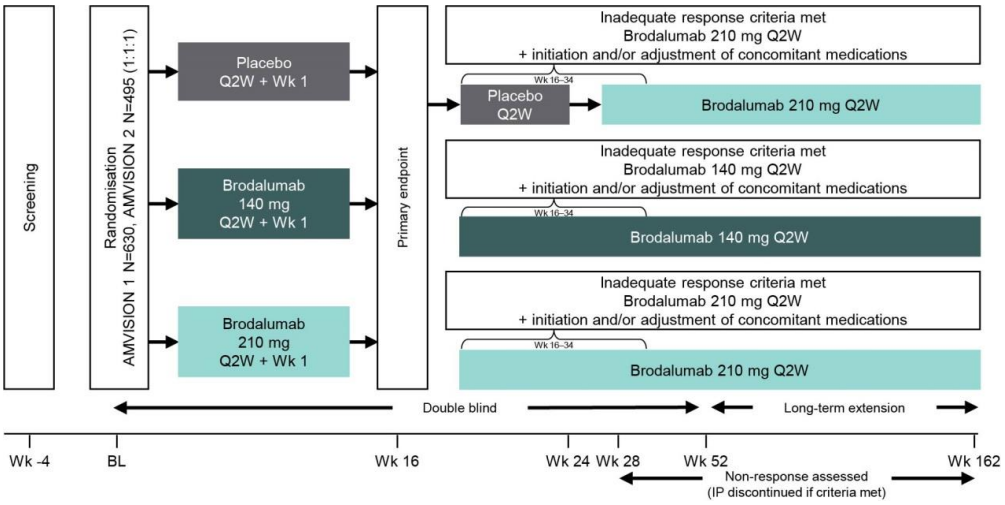
Response, %	**AMVISION-1**			**AMVISION-2**			**Pooled**		
	PBO	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**	**PBO**	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**	**PBO**	**BRO 140 mg Q2W**	**BRO 210 mg Q2W**
Week 16									
ACR20	13.9	39.8***	51.2***	24.7	48.9***	41.8*	19.8	44.8***	46.1***
ACR50	4.1	20.3**	29.8***	8.9	27.7***	22.6*	6.7	24.3***	25.8***
ACR70	2.5	10.2‡	14.9**	3.4	12.8*	10.3‡	3.0	11.6**	12.4***
PASI75	10.3	48.9***	75.3***	10.2	50.0***	65.1***	10.2	49.5***	69.4***
PASI90	7.7	40.0***	64.9***	5.6	34.8***	46.2***	6.5	37.4***	54.1***
PASI100	3.8	20.0*	48.1***	3.7	19.6**	34.0***	3.8	19.8***	39.9***
Dactylitis resolution	20.0	33.3	46.9*	28.2	48.1‡	53.6*	24.6	40.2*	50.4***
Enthesitis resolution	20.5	32.9‡	39.7*	29.2	44.9‡	38.2	25.1	39.1*	38.8*

‡p<0.05 vs placebo; *p<0.01 vs placebo; **p<0.001 vs placebo; ***p<0.0001 vs placebo.

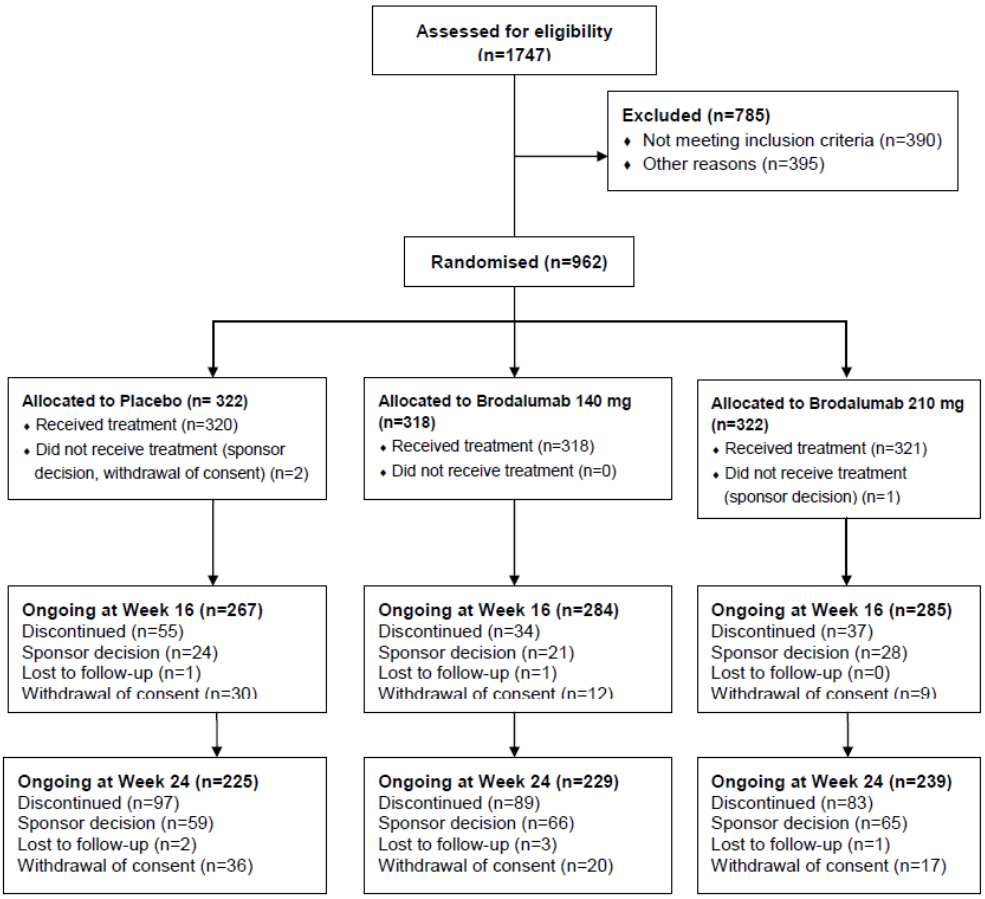
NRI has been applied following early withdrawal from study and at missed visits.

p-values are calculated using a Mantel–Haenszel approach stratified by baseline weight (≤100 kg,>100 kg), prior biologic use (yes/no), baseline PASI score (≤median, >median) and geographical region (North and Latin America, Central and Eastern Europe, Western Europe).

ACR, American College of Rheumatology; BRO, brodalumab; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; Q2W, every 2 weeks.



Supplementary Figure 1 AMVISION-1 and -2 trial design. Q2W, every 2 weeks.



Supplementary Figure 2 Pooled patient disposition for AMVISION-1 and AMVISION-2.

REFERENCES

1. Felson DT, Anderson JJ, Boers M, *et al*. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.