AJM300 (carotegrast methyl), an oral antagonist of α4-integrin, as induction therapy for patients with moderately active ulcerative colitis: a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

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Summary

Background AJM300 is an oral, small-molecule α4-integrin antagonist. We assessed the efficacy and safety of AJM300 in patients with moderately active ulcerative colitis.

Methods This multicentre, randomised, double-blind, placebo-controlled, phase 3 study consisted of two phases: a treatment phase and an open-label re-treatment phase. The study was done at 82 hospitals and clinics in Japan. Patients with a Mayo Clinic score of 6–10, endoscopic subscore of 2 or more, rectal bleeding subscore of 1 or more, and an inadequate response or intolerance to mesalazine were enrolled. Patients were randomly allocated (1:1) via a website to either AJM300 (960 mg) or placebo by the minimisation method, which was adjusted centrally by dynamic assignment against the Mayo Clinic score (≥6 to ≤7, ≥8 to ≤10 points), any use of corticosteroid, anti-TNFα antibody, or immunosuppressants during the disease-active period (yes *vs* no), duration of induction therapy until randomisation (<4 weeks *vs* ≥4 weeks) as the minimisation factors. Patients, investigators, site staff, assessors, and the sponsor were masked to treatment assignments. The study drug was administered orally, three times daily, for 8 weeks, and continued for up to 24 weeks if endoscopic remission was not achieved or rectal bleeding did not stop. The primary endpoint was the proportion of patients with a clinical response at week 8, and was analysed in the full analysis set. Clinical response was defined as a reduction in Mayo Clinic score of 30% or more and 3 or more, a reduction in rectal bleeding score of 1 or more or rectal bleeding subscore of 1 or less, and an endoscopic subscore of 1 or less at week 8. The study is registered with ClinicalTrials.gov, NCT03531892, and is closed to recruitment.

Findings Between June 6, 2018, and July 22, 2020, 203 patients were randomly assigned to AJM300 (n=102) or placebo (n=101). At week 8, 46 (45%) patients in the AJM300 group and 21 (21%) patients in the placebo group had a clinical response (odds ratio 3·30, 95% CI 1·73–6·29; p=0·00028). During the 8-week treatment and 16-week extension treatment periods, adverse events occurred in 39 (39%) of 101 patients in the placebo group and 39 (38%) of 102 patients in the AJM300 group. We found no difference in the incidence of adverse events between groups or after repeated administration of AJM300. The most common adverse event was nasopharyngitis (11 [11%] of 101 patients in the placebo group and ten [10%] of 102 patients in the AJM300 group). The most common treatment-related adverse event was also nasopharyngitis (four [4%] of 101 patients in the placebo group and three [3%] of 102 patients in the AJM300 group). Most adverse events were mild-to-moderate in severity. No deaths were reported. A serious adverse event was reported in the AJM300 group (one patient with anal abscess), but this was judged to be unrelated to study drug.

Interpretation AJM300 was well tolerated and induced a clinical response in patients with moderately active ulcerative colitis who had an inadequate response or intolerance to mesalazine. AJM300 could be a novel induction therapy for the treatment of patients with moderately active ulcerative colitis.

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Introduction

Ulcerative colitis is one of the two major types of inflammatory bowel disease (IBD) alongside Crohn's disease.[1–3] Ulcerative colitis is divided into active and remission stages; symptoms are present in the former stage and are absent in the latter. The disease often has repeated cycles of relapse and remission during its course. The severity of active ulcerative colitis is classified into mild, moderate, and severe, based on clinical symptoms and signs, blood tests, and endoscopy.[4,5] Substantial progress in the treatment of ulcerative colitis has been made during previous decades with the introduction of

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For the Japanese translation of the abstract see Online for appendix 1

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See Online for appendix

Research in context

Evidence before this study

AJM300 is a small-molecule α4-integrin blocker and has been developed as an induction therapy for treatment of patients with moderately active ulcerative colitis, who have an inadequate response or intolerance to mesalazine. We searched PubMed for full reports of clinical trials published in English before Aug 31, 2021, with the terms "ulcerative colitis", "α4-integrin", and "inhibition". Our search identified six reports. One of these was a double-blind, placebo-controlled, phase 2a study of AJM300, which was reported by our group.

Added value of this study

In this randomised, double-blind placebo-controlled, study, AJM300 showed significantly greater induction efficacy compared with placebo in patients with moderately active ulcerative colitis who had an inadequate response or intolerance to oral mesalazine. Favourable therapeutic efficacy with AJM300 was observed for all assessments, including clinical response, symptomatic remission, endoscopic improvement, and endoscopic remission compared with placebo. Furthermore, induction effects were found when AJM300 was re-administered to patients with disease relapses who achieved remission with AJM300. AJM300 had a favourable safety profile in this study, and no cases of progressive multifocal leukoencephalopathy or deaths were observed. AJM300 could be an alternative treatment option for induction therapy in patients with moderately active ulcerative colitis, as it is not a biological and could be used as intermittent or cyclic therapy.

Implications of all the available evidence

Our study showed that oral administration of AJM300 induced a clinical response and endoscopic remission in patients with moderately active ulcerative colitis. AJM300 was well tolerated, and most adverse events were mild to moderate, and manageable. Our results suggest that a maximum of 24 weeks of treatment with AJM300 might be a novel option for induction therapy in patients with moderately active ulcerative colitis who have an inadequate response or intolerance to mesalazine. Re-treatment with AJM300 can be considered in patients who achieved remission with AJM300 but subsequently relapsed.

immunosuppressants, anti-TNFα antibodies, Janus kinase (JAK) inhibitors, anti-interleukin 12/23 p40 antibodies (eg, ustekinumab), and anti-integrin antibodies (eg, vedolizumab).[1–4,6] Choice of treatment should be determined based on disease severity and extent (proctitis, left-sided disease, or extensive disease), the course of the disease during follow-up, and patient preferences.[7–9] The standard pharmacotherapy for mildly to moderately active ulcerative colitis is mesalazine and corticosteroids are used for non-responders to mesalazine or patients with moderately to severely active ulcerative colitis. Use of biologicals, including anti-TNFα antibodies, ustekinumab, and vedolizumab, is recommended for induction and maintenance of remission in moderate-to-severe ulcerative colitis that is either steroid-resistant or steroid-dependent.[6–8]

AJM300 (carotegrast methyl) is a small-molecule α4-integrin antagonist, developed as an induction treatment for patients with moderate ulcerative colitis.[10] The active metabolite of AJM300 inhibits leukocyte extravasation into inflammatory sites by blocking the interaction of α4β1 or α4β7 integrins and their receptors, VCAM-1 and MAd-CAM-1.[10] AJM300 shares the same mechanisms of action as natalizumab,[11] which has not been used in patients with ulcerative colitis, but is approved for the treatment of Crohn's disease in the USA. Natalizumab is associated with a risk of progressive multifocal leukoencephalopathy (PML), a rare opportunistic brain infection caused by John Cunningham virus (JCV). To minimise this risk, treatment with AJM300 has been restricted for the induction of remission in patients with moderately active ulcerative colitis.

Unlike biologicals, AJM300 is not immunogenic, and intermittent or cyclic therapy can be considered in patients who respond to induction therapy with this drug. In a randomised controlled trial of healthy male adults, AJM300 significantly increased circulating lymphocyte counts throughout the day when 960 mg of AJM300 was administered three times daily for 6 days; however, such a finding was not observed with daily doses of 240 mg and 480 mg, suggesting that 960 mg is the optimal dose for further study.[12] In a randomised, double-blind, placebo-controlled, phase 2a study of AJM300,[13] 102 patients with moderately active ulcerative colitis (Mayo Clinic scores of 6–10 points, endoscopic subscore ≥2 points, and rectal bleeding subscore ≥1 point), who had an inadequate response or intolerance to mesalazine or corticosteroids, were randomly assigned to receive AJM300 (960 mg) or placebo three times daily for 8 weeks. In this study, AJM300 showed clinical efficacy in clinical response, clinical remission, endoscopic improvement, and histological improvement, compared with placebo. AJM300 was tolerated well, and no serious adverse events were observed. Here, we report the results of a phase 3 clinical trial to evaluate the efficacy and safety of oral administration of AJM300 in patients with moderately active ulcerative colitis. In this study, we also evaluated re-treatment with AJM300 in patients who relapsed after successful induction with AJM300.

Methods

Study design and participants

This multicentre, randomised, double-blind, placebo-controlled study consisted of two phases: a treatment phase and an open-label re-treatment phase (appendix 2 p 18). The study was done at 82 hospitals and clinics in Japan.

The study protocol and informed consent form were approved by the institutional review board at each participating study site. Outpatients who met the eligibility criteria and agreed to participate in the study were recruited. All patients gave written informed consent before initiation of any study-specific procedures. The study was done in accordance with the ethical principles originating in or derived from the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol is in the appendix 2 (pp 22–204).

Outpatients aged 16–75 years with a diagnosis of moderately active ulcerative colitis with Mayo Clinic scores[14] of 6–10 points, endoscopic subscore of 2 points or greater, and rectal bleeding subscore of 1 point or greater were eligible for enrolment. Patients who had an inadequate response or intolerance to oral mesalazine (sulfasalazine ≥4·0 g, pentasa ≥4·0 g, asacol ≥3·6 g, or lialda ≥4·8 g, per day) were eligible for inclusion. Patients continued to take mesalazine at a constant dose for at least 4 weeks or corticosteroids (prednisolone ≤40 mg or the equivalent per day) for at least 2 weeks before the placebo run-in. Although concomitant mesalazine was administered at a constant dose and regimen throughout the study, the concomitant corticosteroid dose could be tapered by no more than 5 mg every 2 weeks. Patients were ineligible if they had received azathioprine or mercaptopurine within 8 weeks before the placebo run-in, or TNF antagonists, ciclosporin, tacrolimus, methotrexate, or a JAK inhibitor within 12 weeks before the placebo run-in. Any α4-integrin blocker was discontinued 24 weeks before the placebo run-in. Key exclusion criteria were patients with a history of colectomy, a malignant neoplasm, drug hypersensitivity or alcohol dependence, psychiatric symptoms, neurological symptoms, pregnancy or lactation, a white blood cell count of ≤3000 per μL, complications such as leukaemia and lymphoma that present with marked immunosuppression, or concomitant use of immunosuppressants. Full inclusion and exclusion criteria are listed in the appendix 2 (pp 70–82).

Randomisation and masking

Patients were randomly assigned (1:1) to receive either AJM300 (960 mg) or placebo by the minimisation method, which was adjusted centrally by dynamic assignment against the Mayo Clinic score (≥6 to ≤7, ≥8 to ≤10 points), any use of corticosteroid, anti-TNFα antibody, or immunosuppressants during the disease-active period (yes *vs* no), duration of induction therapy until randomisation (<4 weeks *vs* ≥4 weeks) as the minimisation factors. The randomisation sequence was generated independently of the study sponsor. Treatment allocation of patients was initiated via a website using the Randomisation and Trial Supply Management allocation system of Datatrak Enterprise Cloud (NTT DATA; Tokyo, Japan), which determined the eligibility of the registered patient, and assigned allocation sequence and number of the study drug box.

The patients, investigators, site staff, assessors, and the sponsor were masked to treatment assignments. To ensure that masking was maintained, AJM300 and placebo tablets were manufactured so that their appearance was identical. The results of leukocyte fraction measurement were not reported to the investigators and sponsor before the primary analysis. Envelopes were prepared for emergency unmasking.

Procedures

The treatment phase consisted of a 2-week, single-blind placebo run-in period, an 8-week, double-blind treatment period, a 16-week double-blind extension treatment period, and a follow-up period (appendix 2 p 17). Eligible patients entered the single-blind placebo run-in period, during which they received placebo three times daily after meals for 2 weeks to reduce placebo effects. Once eligibility was confirmed at the end of the placebo run-in period, patients received the assigned study drug three times daily after meals for 8 weeks. In the extension treatment period, patients who had no endoscopic remission at week 8 could receive the same treatment for up to 24 weeks until rectal bleeding stopped (rectal bleeding subscore decreased to 0 points) or endoscopic remission occurred (endoscopic subscore became 0). Patients who met the following criteria entered the re-treatment phase: patient completed an 8-week double-blind treatment period; patient attained either a clinical response in the Mayo Clinic score (reduction in the Mayo Clinic score from baseline of ≥30% and ≥3 points, reduction in rectal bleeding subscore from baseline of ≥1 point or rectal bleeding subscore ≤1 point, and endoscopic subscore of ≤1 point) or in the partial Mayo Clinic score (reduction in the partial Mayo Clinic score from baseline of ≥25% and ≥2 points and reduction in rectal bleeding subscore from baseline of ≥1 point or rectal bleeding subscore ≤1 point), rectal bleeding subscore of 0 points, or endoscopic subscore of 0 points at the end of treatment; patient relapsed to moderately active ulcerative colitis; and patient had a 8-week or longer interval between the end of the last dosing and the start of re-administration. Inclusion criteria for entering the extension treatment in the re-treatment phase were: patients completed 8-week treatment with AJM300 and attained a clinical response in the partial Mayo Clinic score, but did not achieve a rectal bleeding subscore of 0 points. Relapse was defined as an increase in the partial Mayo Clinic score of 3 points or greater, a rectal bleeding subscore of 1 point or greater, and the investigator's decision. This re-treatment phase was a single-arm trial of AJM300 in an open-label setting and could be cycled until AJM300 did not show efficacy or was intolerable. During this phase, patients received the same dose and regimen of AJM300 as during the 8-week treatment and extension treatment period if rectal bleeding had not stopped.

Mayo Clinic and partial Mayo Clinic scores were assessed at weeks 0, 8, 24, and weeks 0, 2, 4, 8, 12, 16,

20, and 24, respectively. Endoscopic findings were assessed at week 8, and for as long as possible after week 12. Endoscopic subscores were assessed primarily by on-site investigators. A Central Assessment Committee for endoscopy was established to assure the reliability of the assessment by the on-site investigators. In the re-treatment phase, partial Mayo Clinic score was used for efficacy assessment at every visit after dosing. During the follow-up period, the partial Mayo Clinic score was assessed at weeks 4, 8, 26, and 52 after the end of treatment, during the treatment phase and the re-treatment phase. Laboratory tests, including haematology, blood biochemistry, and urinalysis were assessed at screening, and weeks 0, 2, 4, 8, 12, 16, 20, and 24. Stool samples were collected at screening, and weeks 0, 8, 12, 16, 20, and 24, but not during the re-treatment phase.

Outcomes

The primary endpoint was the proportion of patients with a clinical response at week 8. Key secondary endpoints were the proportion of patients with clinical remission, symptomatic remission, endoscopic improvement, and endoscopic remission at weeks 8 and 24. In patients who had cessation of rectal bleeding or endoscopic remission after treatment with AJM300, time to remission during 24-week treatment in both groups, and time to relapse after the end of treatment were evaluated as a secondary endpoints. All secondary endpoints are listed in the appendix 2 (pp 101–104). Clinical response was defined as a reduction in Mayo Clinic score of 30% or more and 3 or more, a reduction in rectal bleeding score of 1 or more or rectal bleeding subscore of 1 or less, and an endoscopic subscore of 1 or less. Clinical remission was defined as a Mayo Clinic score of 2 points or less and any subscore of greater than 1 point. Symptomatic remission was defined as the total of rectal bleeding subscore and stool frequency subscore of 1 point or less. Endoscopic improvement was defined as an endoscopic subscore of 1 point or less. Efficacy in the re-treatment phase was assessed using partial Mayo Clinic scores. Safety was assessed based on adverse events (according to the ICH E2A guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting[15]), vital signs, CNS symptoms, and clinical tests. CNS symptoms were defined as adverse events of special interest, considering the potential risk of developing PML. JCV antibody was assessed in an exploratory manner at weeks 0, 8, and 24 in the treatment phases, and weeks 0, 8, and 24 in the re-treatment phase. Anti- JCV antibody serological status and index were determined by a two-step, second-generation antibody assay (STRATIFY JCV DxSelect; Focus Diagnostics; Cypress, CA, USA).[16] A Safety Assessment Committee was set up to advise on how to deal with patients with suspected initial symptoms of PML and, if necessary, to ensure safe detection of the onset of PML due to AJM300.

Statistical analysis

The proportion of patients with a clinical response at week 8 was expected to be 50·0% for AJM300 and 30·5% for placebo according to our previous phase 3 study (unpublished data). The sample size estimation (99 patients per group) was based on 80% power to show the superiority of AJM300 over placebo with a χ^2 test (at a significance level of 0·05). Safety analysis was done for patients in the safety analysis set, which consisted of all patients who received the study drug at least once. The primary set for the assessment of efficacy was the full analysis set, which included all patients who had received the study drug at least once and who also had any efficacy data, and secondarily was the per protocol set, which was defined as the subset of patients in the full analysis set after excluding patients who did not meet inclusion criteria, met exclusion criteria, whose adherence was low, or who were untraceable or lacking data.

The Mayo Clinic subscore was calculated from the sum of the four subscores; missing subscores were imputed with the last observation carried forward method, which was adopted under the hypothesis that the data at the time of discontinuation of administration were maintained until 24 weeks thereafter. An endoscopic subscore of 3 points was used as a substitute for endoscopic subscore if endoscopy could not be done at weeks 8 and 24 because of persistence or exacerbation of primary disease. The primary endpoint (odds ratio [OR] and CI) was analysed in the full analysis set by logistic regression, with the proportion of patients with a clinical response at week 8 on the Mayo Clinic score as an objective variable, and the treatment group and stratification factors as explanatory variables. This analysis was done in the per protocol set as a sensitivity analysis. The difference in the proportion of patients with a clinical response between the AJM300 and placebo groups was analysed using the χ^2 test, and the 95% CI was calculated using the Newcombe score method.[17] Additionally, for sensitivity analysis, coordinated analyses were done by adding a new covariate (age, sex, disease duration, or initial/recurrence) to the model of the primary endpoint analysis. Subgroup analyses of the primary endpoint were done. 95% CIs were calculated at week 8 in the placebo and AJM300 groups, and the difference between the groups was analysed using the χ^2 test. For the secondary endpoints, the proportions of patients in clinical remission, symptomatic remission, endoscopic improvement, and endoscopic remission were calculated, and the differences between the AJM300 and placebo groups were analysed using the χ^2 test, with the 95% CI calculated using the Newcombe score method.[17] Cumulative clinical responses were evaluated based on the achievement of a clinical response (assessed by the partial Mayo Clinic score) of at least one at each visit (week 2, 4, 8, 12, 16, 20, and 24). Time to remission and

time to relapse were estimated with the Kaplan–Meier method. For evaluating safety, adverse events were tabulated by treatment group. Adverse events were coded using the Medical Dictionary for Regulatory Activities version 21.0. All statistical tests used a significance level of 5% and were two-sided. All analyses were done using SAS version 9.4 for Windows.

This study is registered with ClinicalTrials.gov, NCT03531892, and recruitment of patients has been completed.

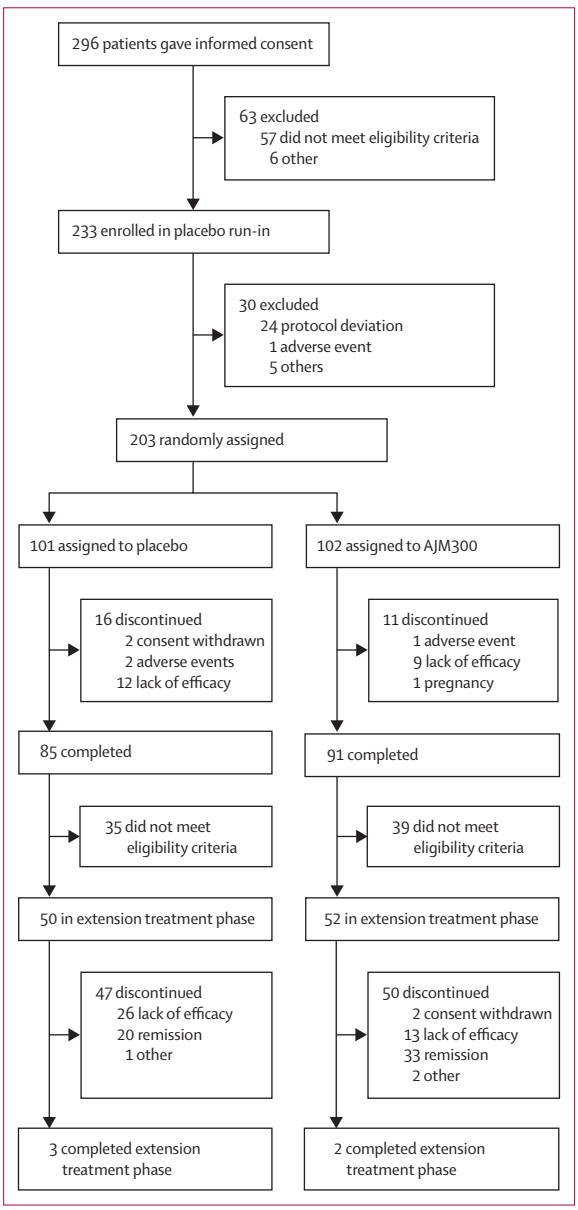

Figure: **Trial profile**
The safety analysis set comprised 101 patients in the placebo group and 102 patients in the AJM300 group. The full analysis set comprised 101 patients in the placebo group and 102 patients in the AJM300 group. The per-protocol set comprised 83 patients in the placebo group and 85 patients in the AJM300 group.

Role of the funding source
EA Pharma was involved in study design, data collection, data analysis, data interpretation, and writing of the report, and made the decision to submit the paper for publication. Kissei Pharmaceutical was involved in data collection.

Results
Between June 6, 2018, and July 22, 2020, 233 (79%) of 296 patients who gave informed consent met the eligibility criteria were entered into the 2-week single-blind placebo run-in period. The analysis cutoff date was May 26, 2021. 203 patients were randomly assigned to receive either AJM300 (n=102) or placebo (n=101; figure). Mean disease duration was 6·1 years (SD 5·6) and mean Mayo Clinic score at week 0 was 7·8 points (1·3; table 1). 188 (93%) of 203 patients had an inadequate

	Placebo (n=101)	AJM300 (n=102)	Total (n=203)
Sex			
Male	59 (58%)	64 (63%)	123 (61%)
Female	42 (42%)	38 (37%)	80 (39%)
Age, years	42·8 (13·3)	44·0 (14·2)	43·4 (13·7)
Bodyweight, kg	63·2 (12·5)	62·8 (11·1)	63·0 (11·8)
Disease duration, years	5·7 (5·7)	6·5 (5·5)	6·1 (5·6)
Mayo Clinic score	7·9 (1·3)	7·7 (1·4)	7·8 (1·3)
6–7	42 (42%)	43 (42%)	85 (42%)
8–10	59 (58%)	59 (58%)	118 (58%)
Partial Mayo Clinic score	5·7 (1·2)	5·7 (1·3)	5·7 (1·3)
≤5	46 (46%)	45 (44%)	91 (45%)
≥6	55 (54%)	57 (56%)	112 (55%)
Disease extent			
Extensive	38 (38%)	39 (38%)	77 (38%)
Left-sided	49 (49%)	48 (47%)	97 (48%)
Proctitis	14 (14%)	15 (15%)	29 (14%)
Previous treatment failure			
Inadequate response to mesalazine	93 (92%)	95 (93%)	188 (93%)
Intolerance to mesalazine	8 (8%)	7 (7%)	15 (7%)
Inadequate response to corticosteroids	9 (9%)	6 (6%)	15 (7%)
Intolerance to corticosteroids	3 (3%)	1 (1%)	4 (2%)
Inadequate response to anti-TNFα agents	1 (1%)	1 (1%)	2 (1%)
Intolerance to anti-TNFα agents	0	1 (1%)	1 (<1%)
Inadequate response to immunosuppressants	1 (1%)	5 (5%)	6 (3%)
Intolerance to immunosuppressants	3 (3%)	4 (4%)	7 (3%)
Treatment in this disease active stage			
Mesalazine (oral)	95 (94%)	98 (96%)	193 (95%)
Mesalazine (topical)	19 (19%)	31 (30%)	50 (25%)
Corticosteroids (oral)	8 (8%)	7 (7%)	15 (7%)
Corticosteroids (topical)	24 (24%)	25 (25%)	49 (24%)
Anti-TNFα agents	1 (1%)	0	1 (<1%)
Immunosuppressants	2 (2%)	5 (5%)	7 (3%)

Data are n (%) or mean (SD). TNF=tumour necrosis factor.

Table 1: **Patient baseline characteristics (full analysis set)**

response to mesalazine, which was confirmed during the screening period, and 15 (7%) of 203 were intolerant to mesalazine. 176 (87%) of 203 patients completed the 8-week, double-blind treatment period, and 102 (50%) patients entered the extension treatment period. Two (2%) of 102 patients in the AJM300 group and three (3%) of 101 patients in the placebo group completed 24-week treatment. Among patients who completed the treatment phase, 37 (21%) of 176 patients with a relapse of disease (25 patients in the AJM300 group and 12 patients in the placebo group) entered re-treatment phase 1 (appendix 2 p 18). 34 of these patients completed 8-week treatment with AJM300, and nine patients entered extension treatment. Four patients continued 24-week treatment with AJM300 in re-treatment phase 1. Re-treatment phase 2 was done in nine patients (eight patients in the AJM300 group and one patient in the placebo group in the treatment phase) who completed re-treatment phase 1. Eight of these patients continued with 8-week treatment with AJM300, and four patients entered extension treatment. One patient received 24-week treatment with AJM300 in re-treatment phase 2. 114 patients received one cycle of treatment with AJM300, 26 patients received a second cycle, and eight patients received a third cycle. The safety and efficacy assessment did not include the third cycle because of the small number of patients. The cumulative mean and median duration of AJM300 administration in 114 patients were 90·8 days (SD 64·7) and 77 days (IQR 56–97), respectively. No patients required dose reduction in this study.

	Number of patients	Improvement		Difference between groups		χ^2 test	
		n (%)	95% CI	%	95% CI	Statistic	p value
Clinical response							
Week 8							
Placebo	101	21 (21%)	14 to 30	24%	11 to 36	13·56	0·00023
AJM300	102	46 (45%)	36to 55	..	..	..	..
Week 24							
Placebo	101	23 (23%)	16 to 32	26%	13 to 38	15·18	<0·0001
AJM300	102	50 (49%)	40 to 59	..	..	..	..
Clinical remission							
Week 8							
Placebo	101	14 (14%)	8 to 22	9%	–2 to 19	2·57	0·11
AJM300	102	23 (23%)	16 to 32	..	..	..	..
Week 24							
Placebo	101	19 (19%)	12 to 28	12%	0 to 23	3·67	0·056
AJM300	102	31 (30%)	22 to 40	..	..	..	..
Symptomatic remission							
Week 8							
Placebo	101	22 (22%)	15 to 31	19%	7 to 31	8·84	0·0029
AJM300	102	42 (41%)	32 to 51	..	..	..	..
Week 24							
Placebo	101	29 (29%)	21 to 38	21%	8 to 34	9·63	0·0019
AJM300	102	51 (50%)	41 to 60	..	..	..	..
Endoscopic improvement							
Week 8							
Placebo	101	27 (27%)	19 to 36	28%	15 to 40	16·66	<0·0001
AJM300	102	56 (55%)	45 to 64	..	..	..	..
Week 24							
Placebo	101	28 (28%)	20 to 37	27%	14 to 39	15·45	<0·0001
AJM300	102	56 (55%)	45 to 64	..	..	..	..
Endoscopic remission							
Week 8							
Placebo	101	3 (3%)	1 to 8	11%	3 to 19	7·65	0·0057
AJM300	102	14 (14%)	8 to 22	..	..	..	..
Week 24							
Placebo	101	7 (7%)	3 to 14	9%	0 to 18	3·87	0·049
AJM300	102	16 (16%)	10 to 24	..	..	..	..

(Table 2 continues on next page)

For the primary endpoint, 46 (45%) of 102 patients in the AJM300 group and 21 (21%) of 101 patients in the placebo group had a clinical response at week 8 (OR 3·30, 95% CI 1·73 to 6·29; p=0·00028). A similar result was obtained in the per-protocol population (appendix 2 p 8). The difference in the clinical response rate between the groups was 24% (95% CI 11 to 36; p=0·00023). Other sensitivity analyses of the primary endpoints were done in the full analysis set by adding one explanatory variable (age, sex, or disease duration) to the logistic regression model of the main analysis, and similar results were obtained (appendix 2 p 8). In a subgroup analysis, AJM300 showed favourable efficacy compared with placebo regardless of severity, disease extent, and disease duration (appendix 2 pp 9–11). The cumulative clinical response assessed by the partial Mayo Clinical score reached a maximum at week 12 in the extension treatment period. With respect to the key secondary endpoints, symptomatic remission, endoscopic improvement, and endoscopic remission also were significantly better with AJM300 than placebo at weeks 8 and 24 (table 2; appendix 2 p 19). The proportions of patients in clinical remission in the AJM300 group at weeks 8 and 24 were not significantly higher than those in the placebo group. 26 patients who relapsed after AJM300 treatment received re-treatment with AJM300, with a clinical response to AJM300 at week 8 in this phase in 19 (73%) patients, assessed according to the partial Mayo Clinic score (appendix 2 p 12). The median time to remission (rectal bleeding subscores of 0 points or endoscopic subscores of 0 points) in the AJM300 and placebo groups were 99 days (95% CI 99–100) and 113 days (104–134), respectively (p<0·0001). Significant increases in peripheral lymphocyte counts from baseline were observed after 2 weeks of treatment with AJM300, whereas no changes were observed in the placebo group (appendix 2 p 20). At week 8, one day after the last administration of AJM300, the effect on peripheral lymphocyte counts attenuated according to disappearance of AJM300 from the plasma. Faecal calprotectin was significantly reduced in the AJM300 group at week 8 compared with placebo (mean 1257 μg/g in the AJM300

group *vs* 2997 μg/g in the placebo group; difference between the groups –1740 μg/g, 95% CI –3380 to –101; p=0·038).

During the 8-week treatment period, 33 (33%) of 101 patients in the placebo group had adverse events, as did 36 (35%) of 102 patients in the AJM300 group. 39 (39%) of 101 patients in the placebo group and 39 (38%) of 102 patients in the AJM300 groups had adverse events during the treatment phase (including the open-label extension treatment period; table 3; appendix 2 pp 13–16). 18 (18%) of 101 patients in the placebo group and 18 (18%) of 102 patients in the AJM300 group had treatment-related adverse events during the treatment phase. The incidence of adverse events and treatment-related adverse events on re-treatment with AJM300 were 11 (42%) of 26 patients and three (12%) of 26 patients, respectively, and no serious adverse events were reported (appendix 2 p 12), suggesting there was no change in safety outcomes after repeated administration of AJM300. The most common adverse event was nasopharyngitis, which was reported in 11 (11%) of 101 patients in the placebo group and ten (10%) of 102 patients in the AJM300 group. The most common treatment-related adverse event was also nasopharyngitis, which was reported in four (4%) of 101 patients in the placebo group and three (3%) of 102 patients in the AJM300 group. The severity of most adverse events was mild to moderate, except in one patient who had headache and pyrexia in the placebo group. No deaths were reported. A serious adverse event was reported in the AJM300 group (one patient with anal abscess), but this was judged to be unrelated to study drug. One case of mild dyskinesia was reported in the AJM300 group during the follow-up period (around 9 months after the last dose), but it was adjudicated that the onset of PML could be ruled out by the Safety Assessment Committee. Adverse events leading to treatment discontinuation occurred in two patients in the placebo group (ulcerative colitis and vomiting in one patient each) and two patients in the AJM300 group (drug hypersensitivity and abnormal sensation in one patient each). In the re-treatment phase, one patient discontinued treatment because of ulcerative colitis (appendix 2 p 12).

146 (73%) of 199 patients were seropositive at baseline for anti-JCV antibodies. No significant increase in the anti-JCV antibody index was observed at weeks 8 and 24 in either group (appendix 2 p 21). In the placebo group, two (7%) of 27 patients were negative for anti-JCV antibodies at baseline and were positive at week 8; two (13%) of 16 patients were positive at week 24. In the AJM300 group, four (16%) of 25 patients who were negative at baseline were positive for anti-JCV antibodies at week 8 and one (8%) of 13 patients was positive at week 24. In the AJM300 group, increases in white blood cell count and leukocyte fraction, including eosinophil, basophil, lymphocyte, and monocyte counts, were observed but no such increases were seen in the placebo group (data not shown). There were no clinically significant abnormalities in any other clinical tests and vital signs.

	Number of patients	Improvement		Difference between groups		χ^2 test	
		n (%)	95% CI	%	95% CI	Statistic	p value
(Continued from previous page)							
Rectal bleeding disappearance							
Week 2							
Placebo	101	7 (7%)	3 to 14	7%	–2 to 16	2·53	0·11
AJM300	102	14 (14%)	8 to 22	..	..	..	..
Week 4							
Placebo	101	12 (12%)	7 to 20	22%	11 to 33	14·35	0·00015
AJM300	102	35 (34%)	26 to 44	..	..	..	..
Week 8							
Placebo	101	25 (25%)	17 to 34	19%	6 to 32	8·42	0·0037
AJM300	102	45 (44%)	35 to 54	..	..	..	..
Week 12							
Placebo	101	23 (23%)	16 to 32	29%	16 to 41	18·46	<0·0001
AJM300	102	53 (52%)	42 to 61	..	..	..	..
Week 16							
Placebo	101	26 (26%)	18 to 35	26%	13 to 38	14·67	0·00013
AJM300	102	53 (52%)	42 to 61	..	..	..	..
Week 20							
Placebo	101	26 (26%)	18 to 35	26%	13 to 38	14·67	0·00013
AJM300	102	53 (52%)	42 to 61	..	..	..	..
Week 24							
Placebo	101	27 (27%)	19 to 36	26%	13 to 38	14·54	0·00014
AJM300	102	54 (53%)	43 to 62	..	..	..	..
Cumulative clinical response on the partial Mayo Clinic score							
Week 2							
Placebo	101	13 (13%)	8 to 21	17%	5 to 27	8·32	0·0039
AJM300	102	30 (29%)	21 to 39	..	..	..	..
Week 4							
Placebo	101	26 (26%)	18 to 35	27%	14 to 39	15·72	<0·0001
AJM300	102	54 (53%)	43 to 62·	..	..	..	..
Week 8							
Placebo	101	38 (38%)	29 to 47	25%	11 to 38	12·81	0·00034
AJM300	102	64 (63%)	53 to 72	..	..	..	..
Week 12							
Placebo	101	41 (41%)	32 to 50	29%	15 to 41	17·27	<0·0001
AJM300	102	71 (70%)	60 to 78	..	..	..	..
Week 16							
Placebo	101	41 (41%)	32 to 50	29%	15 to 41	17·27	<0·0001
AJM300	102	71 (70%)	60 to 78	..	..	..	..
Week 20							
Placebo	101	41 (41%)	32 to 50	29%	15 to 41	17·27	<0·0001
AJM300	102	71 (70%)	60 to 78	..	..	..	..
Week 24							
Placebo	101	41 (41%)	32 to 50	29%	15 to 41	17·27	<0·0001
AJM300	102	71 (70%)	60 to 78	..	..	..	..

Table 2: **Summary of efficacy endpoints in the treatment phase (full analysis set)**

Discussion

	Placebo (n=101)	AJM300 (n=102)
Adverse events	39 (39%)	39 (38%)
Treatment-related adverse events	18 (18%)	18 (18%)
Death	0	0
Serious adverse events except for death	3 (3%)	1 (1%)
Adverse events leading to discontinuation	2 (2%)	2 (2%)
Severe adverse events	1 (1%)	0
Adverse events (≥2% in any group)		
Nasopharyngitis	11 (11%)	10 (10%)
Influenza	3 (3%)	1 (1%)
Bronchitis	0	2 (2%)
Headache	2 (2%)	3 (3%)
Oropharyngeal pain	0	2 (2%)
Upper respiratory tract inflammation	2 (2%)	1 (1%)
Nausea	0	3 (3%)
Stomatitis	1 (1%)	2 (2%)
Upper abdominal pain upper	4 (4%)	1 (1%)
Abnormal hepatic function	1 (1%)	2 (2%)
Rash	2 (2%)	1 (1%)
Increased blood lactate dehydrogenase	2 (2%)	0
Treatment-related adverse events (≥2% in any group)		
Nasopharyngitis	4 (4%)	3 (3%)
Influenza	2 (2%)	0
Headache	1 (1%)	2 (2%)
Nausea	0	2 (2%)
Upper abdominal pain	2 (2%)	0
Abnormal hepatic function	1 (1%)	2 (2%)
Rash	2 (2%)	1 (1%)

AEs in the re-treatment phase are not shown in this table.

Table 3: **Summary of adverse events reported during the treatment phases (safety analysis set)**

In this randomised, double-blind, placebo-controlled, study, AJM300 showed significantly greater induction efficacy compared with placebo in patients with moderately active ulcerative colitis. Efficacy was observed when AJM300 administration was continued up to 24 weeks in patients who did not achieve endoscopic remission within the 8-week treatment period. AJM300 also had significantly better induction efficacy in terms of symptomatic remission, endoscopic improvement, and endoscopic remission, compared with placebo. In a previous phase 3 study, the placebo effect was too large to confirm the efficacy of AJM300 (unpublished data); however, the placebo effect was significantly reduced by adding a placebo run-in period in this study. Pharmacological effects of AJM300 have been confirmed, with increased peripheral lymphocyte counts, a biomarker of α4-integrin antagonist activity,[12] and decreased faecal calprotectin, a sensitive biomarker of IBD.[18] In this study, peripheral lymphocytes were increased in patients who did not respond clinically to AJM300. Therefore, it is unlikely that the lack of clinical response was caused by an insufficient dose of AJM300. Factors causing non-response have not been identified, but could be due to differences in pathological mechanisms of ulcerative colitis. To our knowledge, this is the first study in which an oral, small-molecule α4-integrin antagonist has shown clinical benefits in patients with moderately active ulcerative colitis. An oral α4β7 integrin antagonist is also under development for the treatment of ulcerative colitis.[19] Although ulcerative proctitis was excluded from our previous phase 2 study,[13] this subtype was included in this study, since AJM300 might be used for the treatment of moderately active ulcerative colitis in patients who have an inadequate response or intolerance to oral mesalazine, which also includes ulcerative proctitis in the real world. The 8-week treatment period was designed according to our previous study.[13] However, vedolizumab, an anti-α4β7 heterodimer monoclonal antibody, induced its maximum induction effect in patients with mild to moderate ulcerative colitis after around 16–24 weeks of treatment.[20] Therefore, to determine the optimal treatment duration with AJM300, administration could be continued for up to 24 weeks, with 12-week treatment found to achieve a maximum cumulative effect. Furthermore, the median time to complete induction therapy with AJM300 was around 14 weeks, which was significantly faster than with placebo. Oral and topical mesalazine have been a standard treatment for the induction and maintenance of remission in patients with mild to moderate ulcerative colitis for more than 60 years.[4,21] Corticosteroids are also a mainstay of induction therapy, used with mesalazine in the active stage for patients with ulcerative colitis.[22] However, safety concerns limit the use of corticosteroids; furthermore, about half of patients became refractory or dependent on corticosteroids within 1–2 years.[22–24] The 52-week follow-up in our study is ongoing, but at interim analysis the median time to relapse was 297 days (95% CI 170·0 to not reached) after remission (rectal bleeding subscore of 0 points or endoscopic subscore of 0 points) with AJM300. During the follow-up period after the end of treatment with AJM300 in all phases, mesalazine was the medication most used as maintenance therapy. Furthermore, re-treatment with AJM300 in patients who relapsed after successful induction treatment with AJM300 induced a clinical response in at least 70% of patients, without any increase in safety concerns. Non-responders to AJM300 after re-treatment were patients with worsening of an anal abscess, low white blood cell counts, and *Clostridioides difficile* infection. The number of cycles used for re-treatment has not been fully evaluated because of the small number of patients in our study, but re-treatment with AJM300 might be effective and safe in patients who achieve remission with AJM300 but subsequently relapse. These results indicate that a maximum of 24 weeks of treatment with

AJM300 might be a novel option for induction therapy in patients with moderately active ulcerative colitis, particularly for patients with an inadequate response or intolerance to mesalazine.

The safety profile of AJM300 was similar to that of placebo. A cumulative, dose-dependent increase in adverse events was not observed with an increasing number of administrations in the treatment and re-treatment phases. Mild dyskinesia was reported in one patient in the AJM300 group after the end of dosing as an adverse event of special interest, but it was judged that the onset of PML could be ruled out. PML is an opportunistic CNS infection caused by JCV, and an adverse event of chief concern with natalizumab treatment.[25] However, with the selective α4β7 integrin blocker vedolizumab, few cases of PML have been reported to date.[26,27] Although no cases have yet been reported in patients receiving AJM300, the possibility of PML cannot be completely ruled out for AJM300. There are three risk for natalizumab-associated PML: presence of anti-JCV antibodies, use of immunosuppressants before initiating natalizumab treatment, and duration of treatment.[11] Schwab and colleagues[28] reported that natalizumab increased levels of JCV antibody. The risk of PML increased markedly when the anti-JCV antibody index increased to over 1·5.[29,30] By contrast, AJM300 had no effect on anti-JCV antibody levels after 8 weeks and 24 weeks of treatment, as with placebo. Nor was an increase in anti-JCV antibody observed, including in patients who received AJM300 re-treatment (data not shown). With respect to the risk of PML derived from previous treatment with immunosuppressants, concomitant use of immunosuppressants was prohibited and patients with severe immunosuppression were excluded from our study. Finally, the risk of PML increased with increasing treatment duration with natalizumab, with the greatest increase in risk occurring after 2 years of therapy (1·99 per 1000 in patients with multiple sclerosis).[11] The incidence of PML during initial 1-month to 12-month treatment was much less (0·04 per 1000 patients).[11] Peripheral blood lymphocyte counts that increased with 6 months of treatment with natalizumab recovered to baseline within 4 months after the last administration,[31] and the decreased CD4 to CD8 ratio in the cerebrospinal fluid recovered within 2 months after peripheral blood lymphocytes returned to normal levels, suggesting 6 months were required to remove the pharmacological effects of natalizumab from the body.[32] However, the increase in peripheral blood lymphocyte count seen after administration of AJM300 recovered to baseline levels within 24 h after the last dose, which was quicker than with natalizumab. Therefore, an 8-week interval or longer for the induction cycle used with AJM300 is sufficient to remove the pharmacological activities of AJM300. Furthermore, short-acting AJM300 is a convenient drug that can be used without concerns about anti-drug antibody production or an increased risk of infection, which are both problems associated with intermittent treatment with biologicals.[33] The risk of PML was minimised by limiting the treatment period to a maximum of 6 months and instituting a drug holiday of at least 8 weeks before re-treatment. Taken together, our findings suggest that AJM300 can be used as a substitute for corticosteroids in induction therapy. It would be ideal if remission could be maintained with mesalazine after induction with AJM300. Studies that evaluate the frequency of relapse after induction therapy with AJM300 are needed, but use of immunosuppressants as a maintenance therapy after induction with AJM300 and the switch to biologicals should be considered if frequent relapses occur after a drug holiday from AJM300.

There are some limitations to this study. First, the number of enrolled patients and number of cycles of re-treatment with AJM300 were small. To establish AJM300 as a novel induction therapy, large-scale, long-term, post-marketing surveillance is needed. Second, clinical benefits in patients with severe, active ulcerative colitis or those with an inadequate response or intolerance to corticosteroids, immunosuppressants, and anti-TNFα antibodies have not been evaluated. Third, the re-treatment phase was open label. Some degree of efficacy and safety was observed, but these findings are not robust. A randomised, double-blind, controlled study might be required.

In conclusion, oral administration of the small-molecule α4-integrin antagonist AJM300 induced clinical response and endoscopic remission in patients with moderately active ulcerative colitis who had an inadequate response or intolerance to mesalazine. AJM300 was effective and safe when it was re-administered to patients whose disease relapsed after treatment with AJM300. AJM300 was well tolerated, and most adverse events were mild to moderate and manageable. AJM300 could be a novel option for induction therapy in patients with moderately active ulcerative colitis, who have an inadequate response or intolerance to oral mesalazine. Induction treatment can be repeated when patients relapse after successful induction with AJM300. Further trials could help corroborate these findings.

Contributors

KM contributed to data interpretation and writing of the first draft of the manuscript. MW and TH contributed to the study design, data interpretation, and were responsible for clinical trial management. AO did the analysis of the data. TK wrote the study protocol and contributed to writing the first draft of the manuscript. All authors, except HM, SK, and YM, contributed to data collection. KM, MW, TO, KN, TI, YI, KKa, KKo, FH, KW, AO, TK, and TH provided clinically important advice on feasible inclusion and exclusion criteria. All authors reviewed the draft and approved the final version of the manuscript for publication. MW, AO, and TK are responsible for directly accessing and verifying all data. All had full access to all the data in the study and agree to accept responsibility for the decision to submit for publication.

Declaration of interests

KM has received research support and lecture or consulting fees from AbbVie, EA Pharma, Mitsubishi Tanabe, Mochida, Kyorin, Kissei, JIMRO, Janssen, Pfizer, Takeda, Zeria, Gilead Sciences, Miyarisan, Nippon Kayaku, Celltrion, Eli Lilly, Bristol-Myers Squibb, and Boehringer Ingelheim. MW has received research support and lecture or consulting

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Data sharing

The statistical analysis plan will be shared with those who request data sharing. Requests for data should be directed to the corresponding author. Requests will be reviewed, and scientifically sound proposals will be approved by the study sponsors (EA Pharma and Kissei Pharmaceutical). Additionally, an agreement for data sharing needs to be contracted between data requestors and the sponsors. Data will be shared 2 years after Article publication.

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