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ORIGINAL ARTICLE

A phase 4, randomized, head-to-head trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of fumaric acid esters in adults with moderate-to-severe plaque psoriasis (CHANGE)

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Abstract

Background Brodalumab is a fully human monoclonal immunoglobulin IgG2 antibody that binds to the human IL-17 receptor subunit A and by that inhibits the biologic action of IL-17A, IL-17F, IL-17C and IL-17E. Therapy with fumaric acid esters (FAE) is a well established and widely used first-line systemic treatment for subjects with moderate-to-severe plaque psoriasis.

Objectives To compare brodalumab to FAE in terms of clinical efficacy, patient-reported outcomes and safety in subjects with moderate-to-severe plaque psoriasis who were naïve to systemic treatment.

Methods Eligible subjects were randomized 1 : 1 to 210 mg brodalumab injections or oral FAE according to product label in this 24-week, open-label, assessor-blinded, multi-centre, head-to-head phase 4 trial. The primary endpoints were having PASI75 and having sPGA score of 0 or 1 (sPGA 0/1). Subjects with missing values for the primary endpoints were considered non-responders.

Results A total of 210 subjects were randomized. 91/105 subjects completed brodalumab treatment and 58/105 subjects completed FAE treatment. At Week 24, significantly more subjects in the brodalumab group compared to the FAE group had PASI75 (81.0% vs. 38.1%, $P < 0.001$) and sPGA 0/1 (64.8% vs. 20.0%, $P < 0.001$). In the brodalumab group, the median time to both PASI75 and to PASI90 was significantly shorter than in the FAE group (4.1 weeks vs. 16.4 weeks, and 7.4 weeks vs. 24.4 weeks, respectively, $P < 0.0001$ for both). The rate of adverse events was lower in subjects treated with brodalumab compared to subjects treated with FAE (616.4 vs. 1195.8 events per 100 exposure years). No new safety signals were detected for brodalumab.

Conclusions Brodalumab was associated with rapid and significant improvements in signs and symptoms of moderate-to-severe plaque psoriasis, with a superior efficacy profile to what was observed with FAE in systemic-naïve subjects over 24 weeks.

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Conflicts of interest

A. Pinter has received honoraria as investigator and/or for consultancy and/or received speakers honoraria and/or research grants from AbbVie, Almirall Hermal, Amgen, Biogen Idec, BioNTech, Boehringer Ingelheim, Celgene, GSK, Eli Lilly, Galderma, Hexal, Janssen, LEO Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi Genzyme, Schering-Plough and UCB Pharma. M. Hoffmann has received honoraria as investigator and/or for consultancy and/or

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Introduction

When choosing a suitable and evidence-based systemic first-line treatment for patients with moderate-to severe psoriasis, direct head-to-head (H2H) comparisons are of value. Therefore, the CHANGE trial set out to compare the efficacy of brodalumab with that of fumaric acid esters (FAE, Fumaderm®) in systemic-naïve subjects with moderate-to-severe psoriasis in a multi-centre, assessor-blinded, randomized, active-controlled H2H trial.

While the other currently available interleukin 17 (IL-17) inhibitors secukinumab and ixekizumab bind directly to IL-17A, brodalumab is a fully human monoclonal immunoglobulin G2 (IgG2) antibody that binds to the IL-17 receptor subunit A (IL-17RA) and by that inhibits the biologic action of IL-17A, IL-17F, IL-17C and IL-17E.[1] Brodalumab has shown a rapid onset of action and high complete clearance rates in Phase 3 trials.[2] To date, it is approved for the treatment of moderate-to-severe plaque psoriasis in adult patients in EU, Japan, Taiwan, Thailand, Canada and USA.

Fumaric acid esters (Fumaderm®) is a mixture of dimethyl fumarate (DMF) and monoethyl fumarate salts and has been available in Germany since 1994 and is a well established and widely used first-line systemic treatment for moderate-to-severe plaque psoriasis.[3,4] In Europe, Skilarence® (Almirall, Spain), a product containing only DMF, is approved for treatment of moderate-to-severe plaque-type psoriasis. Therefore, it was relevant to compare FAE and brodalumab, as has also been done for other biologic treatments in plaque psoriasis.[5–8] FAE was recommended as an appropriate comparator by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) in Germany for targeted therapies with first-line label, such as brodalumab,[9] and the present trial was designed in accordance with advice from its health technology assessment committee.

Materials and methods

Subjects

Adults aged ≥18 years diagnosed with moderate-to-severe plaque psoriasis, defined as Psoriasis Area and Severity Index (PASI) >10, affected body surface area (BSA) >10%, and Dermatology Life Quality Index (DLQI) >10, for ≥6 months and who were naïve to systemic treatment for psoriasis were eligible to participate. Key exclusion criteria were history of Crohn's disease or current gastrointestinal disease, history of depressive disorder, history of suicidal ideation and behaviour (SIB) based on the screening tool electronic Colombia-Suicide Severity Rating (eC-SSRS), moderate-to-severe depression based on score ≥10 in the Patient Health Questionnaire 8 (PHQ-8), treatment with phototherapy, or any biologic or other systemic immune modulating treatment for an indication other than psoriasis. All subjects received written and verbal information and gave written informed consent before any trial-related activities.

Trial design and treatments

This was a 24-week, phase 4, randomized, assessor-blinded, multi-centre, open-label, parallel-group, active-controlled trial conducted between November 2017 and March 2019 at 30 sites in Germany. Two hundred tensubjects were randomized 1 : 1 using an interactive web response system (Bioclinica Trident, Princeton, NJ, USA) to receive either subcutaneous, self-administered injections of 210 mg brodalumab once weekly at weeks 0, 1 and 2 followed by 210 mg every 2 weeks, or to FAE tablets (Fumaderm® Initial/Fumaderm®, Biogen GmbH, Munic, Germany) up to 240 mg three times daily, with individual dose titration according to label. The trial was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. The clinical trial protocol was approved by the

independent ethics committee in Germany prior to any subject screening. The trial was registered with EudraCT (2016-003867-21) and Clinicaltrials.gov (NCT03331835, full trial protocol available). Trial design is presented in Fig. 1 and objectives and corresponding endpoints are presented in Table 1.

Assessments

Eligible subjects visited the trial site at Weeks 0, 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24. Assessment of PASI, static Physician's Global Assessments (sPGA), BSA and Nail Psoriasis Severity Index (NAPSI) were performed by investigators blinded to the trial treatment. The NAPSI assessment tool is a score scale of 0–8 for each nail; however, if target nail NAPSI (tNAPSI) is calculated, a score of 0–32 for each nail can be used. Then, the target nail is divided into 4 quarters and a score of 0–8 for each quarter is calculated, bringing the total tNAPSI score to 0–32.[10] In this trial, subjects with tNAPSI ≥6 of any nail at baseline had the nail with the most severe tNAPSI score followed until Week 24. The

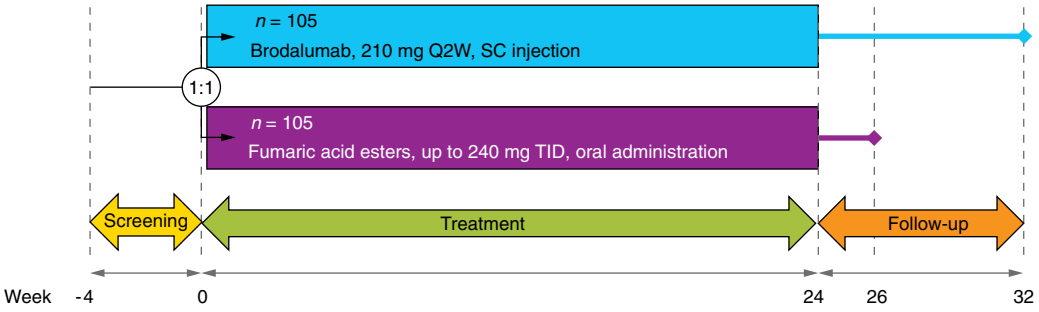

Figure 1 CHANGE trial design. At Week 0, subjects were randomized 1 : 1 with stratification by baseline weight (<100 or ≥100 kg) and treated with either subcutaneous injections of 210 mg brodalumab once weekly at Weeks 0, 1 and 2 followed by 210 mg every 2 weeks, or oral fumaric acid esters up to 240 mg three times daily. Treatment period was 24 weeks and follow-up period 8 weeks for brodalumab-treated subjects and 2 weeks for fumaric acid ester-treated subjects. Q2W, every 2 weeks; SC, subcutaneous, TID, 3 times daily.

Table 1 Efficacy objectives and endpoints in the CHANGE trial

Primary objective	Endpoints
To compare the efficacy of brodalumab to that of FAE in subjects with moderate-to-severe plaque psoriasis who were naïve to systemic treatment	**Primary endpoints**
	Having at least PASI75 at Week 24
	Having sPGA 0/1 at Week 24
	Secondary endpoints
	Having PASI90 at Week 24
	Having PASI100 at Week 24
	Change from baseline at Week 24 in PASI score
	Per cent change from baseline at Week 24 in PASI score
	Change from baseline at Week 24 in affected BSA
Secondary objective	**Secondary endpoints**[†]
To compare the effect on patient-reported outcomes of brodalumab to that of FAE in subjects with moderate-to-severe plaque psoriasis	Change from baseline to Week 24 in DLQI total score
	Having DLQI 0/1 at Week 24
Exploratory objective	**Exploratory endpoint**
To explore the effect of brodalumab vs. that of FAE on nail involvement in subjects with moderate-to-severe plaque psoriasis and a tNAPSI score of ≥6 on target nail	Change from baseline at Week 24 in tNAPSI total score

Protocol-defined objectives and endpoints related to efficacy are presented.
BSA, body surface area; DLQI 0/1, Dermatology Life Quality Index score of 0 or 1; FAE, fumaric acid esters; tNAPSI, target nail Nail Psoriasis Severity Index; PASI75/90/100, 75%/90%/100% improvement from baseline in Psoriasis Area and Severity Index; PSI, Psoriasis Symptom Inventory; sPGA 0/1, static Physician's Global Assessment score of 0 or 1.
[†]Four secondary endpoints related to the patient-reported outcome Psoriasis Symptom Inventory (PSI) were also defined in the protocol. Due to technical challenges with the eDiary devices distributed to subjects, the data collected were not of sufficient quality for analysis. Therefore, these endpoints are not included in this report.

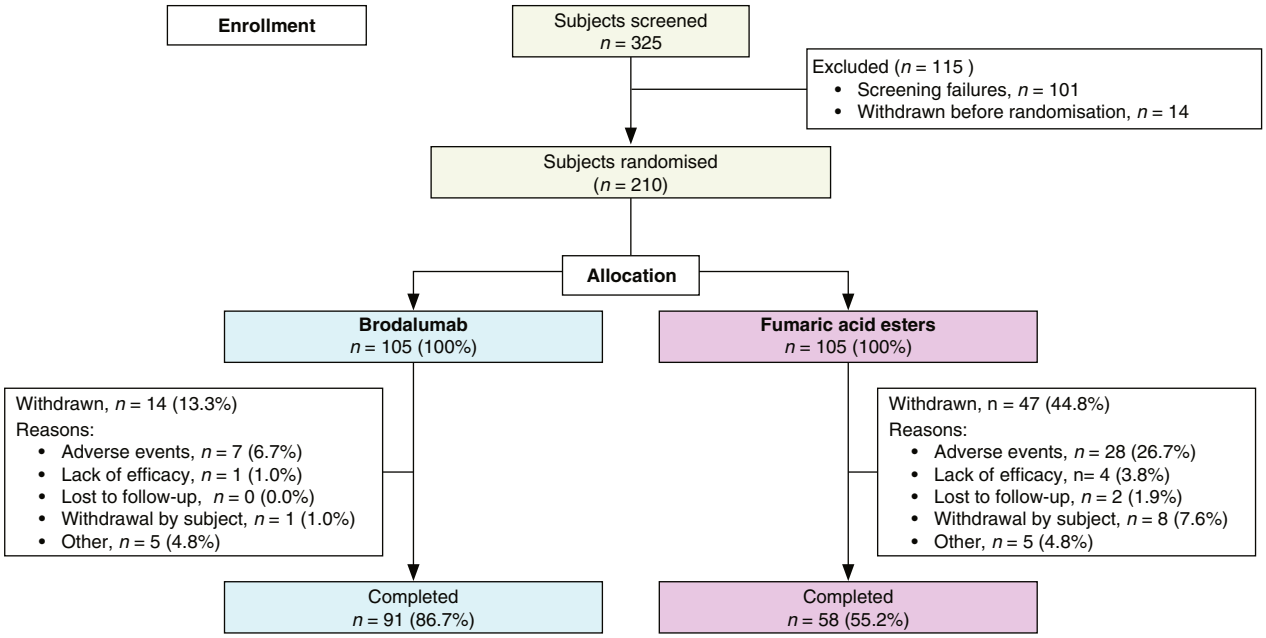

Figure 2 Subject disposition. Adapt colors as sent file (RGB)

patient-reported outcome (PRO) efficacy assessment DLQI was performed first at a trial visit. The eC-SSRS for SIB and the PHQ-8 for depression were performed as the last assessment before administration of trial treatment. They were performed at every visit (PHQ-8 not at Weeks 1 and 3). PHQ-8 scores ≥10 (the cut-off point for moderate depression) were reported adverse event (AEs) and the subject referred to a mental health professional. In case of PHQ-8 score ≥15 (the cut-off point for moderate-to-severe depression), the subject was additionally withdrawn from the trial. The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used for coding of AEs.

Statistical analyses

Statistical analysis was carried out using SAS (Heidelberg, Germany) version 9.4. With an assumed drop-out rate of 50% in the FAE group and <40% in the brodalumab group, a sample size of 105 subjects in each group was considered sufficient to detect a difference between brodalumab and FAE for the primary endpoints with a power of 80%. The sample size was determined using Fisher's exact test for the two independent proportions under the assumption of a two-sided test of 5%.

Efficacy endpoints were analysed for the intention-to-treat population (full analysis set). Safety data were analysed for subjects who were exposed to trial treatment and according to the treatment received (safety analysis set). All significance tests were two-sided using a significance level of 5%. No correction for multiplicity was performed.

Binary data were analysed using the Cochran–Mantel–Haenszel (CMH) test with stratification by weight group (≥100 or <100 kg) and non-responder imputation for missing data. Sensitivity analyses were performed on the primary endpoints: a logistic regression model with baseline score and weight group and a repetition of primary analysis (CMH test). Mixed model for repeated measurements (MMRM) or last observation carried forward (LOCF) method was used to impute missing data. Continuous data were analysed using MMRM, including treatment group, week, interaction between treatment and time, baseline score and baseline weight group as fixed factors. The MMRM model was the prespecified method used to model missingness under the missing at random assumption. As a sensitivity analysis and to facilitate comparison to other trials, an analysis using LOCF method for missing data was also performed on continuous data. Time-to-response data were analysed using Cox regression.

Results

Trial population

A total of 210 subjects were randomized, 105 to brodalumab and 105 to FAE (Fig. 2). 104 and 102 subjects were exposed to brodalumab and FAE, respectively. Baseline characteristics were comparable between the two groups (Table 2). At baseline, 81 subjects (38.6%) had nail psoriasis; 43 subjects (41.0%) in the brodalumab group and 38 subjects (36.2%) in the FAE group.

Fourteen subjects (13.3%) in the brodalumab group and 47 subjects (44.8%) in the FAE group withdrew from the trial (Fig. 2).

Efficacy assessments

Brodalumab was superior to FAE for both primary endpoints, PASI75 and sPGA 0/1. At Week 24, 81.0% of subjects in the brodalumab group had PASI75 compared with 38.1% of subjects in the FAE group ($P < 0.001$), and 64.8% of subjects in the brodalumab group had sPGA 0/1 compared with 20.0% of subjects in the FAE group ($P < 0.001$; Table 3, Fig. 3). The outcome of the primary endpoints was confirmed by sensitivity analyses (Table S1, Supporting Information). Brodalumab was also superior to FAE in terms of PASI90 and PASI100 response (Table 3, Fig. 3). The median times to PASI75 and PASI90 response were both significantly shorter in the brodalumab group than in the FAE group (4.1 weeks vs. 16.4 weeks and 7.4 weeks vs. 24.4 weeks, respectively, $P < 0.0001$ for both). Recently, having a low absolute PASI (aPASI) corresponding to clear or almost clear skin was recommended as a relevant treatment goal for psoriasis.[11] A post hoc analysis showed superiority of brodalumab in terms of both PASI ≤ 3 and PASI ≤ 1 (Table 3, Fig. 3). More subjects in the brodalumab groups had DLQI 0/1 at Week 24, indicating that fewer brodalumab-treated subjects had impairment of health-related quality of life (QoL; Table 3 and Fig. 3).

The mean aPASI score was significantly lower in the brodalumab group than the FAE group at Week 24 (Table 4, Fig. 4). The estimated mean aPASI varies between analyses made with LOCF and MMRM imputation of missing data (Table 4).

At Weeks 12 and 24, the observed mean tNAPSI score was lower in the brodalumab group than in the FAE group (Table 4, Fig. 5), and the observed relative change from baseline in tNAPSI score was greater in the brodalumab group than in the FAE group (Table 4). Brodalumab was superior to FAE in absolute change from baseline in tNAPSI score, both when missing data were imputed using MMRM and LOCF (Table S2, Supporting Information). tNAPSI data should be interpreted with caution due to the low number of subjects with tNAPSI data.

Brodalumab was also superior to FAE in absolute change from baseline in PASI score, relative improvement from baseline in PASI score, absolute change from baseline in BSA and absolute change from baseline in DLQI score at Week 24, both when MMRM and LOCF were used to impute missing data (Table S2, Supporting Information).

Table 2 Subject demographics and baseline disease characteristics

Characteristic	Brodalumab *N* = 105	FAE *N* = 105	Total *N* = 210
Demographics			
Age, years (mean ± SD)	44.0 ± 14.3	43.9 ± 13.9	43.9 ± 14.1
Sex [*n* (%)]			
Female	32 (30.5%)	33 (31.4%)	65 (31.0%)
Race			
Asian [*n* (%)]	1 (1.0%)	0 (0.0%)	1 (0.5%)
White [*n* (%)]	104 (99.0%)	105 (100.0%)	209 (99.5%)
Weight, kg (mean ± SD)	87.8 ± 20.4	86.6 ± 21.2	87.2 ± 20.7
Weight group ≥100 kg			
n	26	26	52
kg, mean ± SD	116 ± 13.2	115 ± 13.9	116 ± 13.4
BMI, kg/m^2 (mean ± SD)	28.5 (5.7)	28.0 ± 6.0	28.2 ± 5.9
Psoriasis duration and severity			
Duration (mean years ± SD)	14.3 ± 11.5	13.2 ± 11.7	13.7 ± 11.6
PASI score (mean ± SD)	17.2 ± 5.9	17.8 ± 6.7	17.5 ± 6.3
Moderate [10–19, *n* (%)]	79 (75.2%)	74 (70.5%)	153 (72.9%)
Severe [≥20, *n* (%)]	26 (24.8%)	31 (29.5%)	57 (27.1%)
sPGA score (mean ± SD)	3.5 ± 0.6	3.5 ± 0.7	3.5 ± 0.6
BSA score (mean ± SD)	24.8 ± 15.2	25.5 ± 14.9	25.2 ± 15.1
tNAPSI score† [mean ± SD (*n*)]	6.4 ± 4.4 (43)	7.7 ± 4.9 (38)	7.0 ± 4.7 (81)
DLQI score (mean ± SD)	18.8 ± 5.2	18.5 ± 4.9	18.7 ± 5.1

BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; FAE, fumaric acid esters; *N*, number of subjects randomised; *n*, number of subjects with a measurement; tNAPSI, target nail Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician's Global Assessment.
†tNAPSI data only collected from subjects who had nail psoriasis at baseline.

Table 3 Binary and time-to-response efficacy results

Binary assessments at Week 24†	Estimated mean responder rate (%)		Estimated rate difference (%)	95% CI	*P*-value
	Brodalumab	FAE			
PASI75†	81.0	38.1	42.9	30.9, 54.8	<0.001
sPGA score 0 or 1†	64.8	20.0	44.8	32.8, 56.7	<0.001
PASI90†	65.7	21.9	43.8	31.8, 55.8	<0.001
PASI100†	40.0	8.6	31.4	20.8, 42.1	<0.001
Proportion of subjects with PASI ≤3†	79.0	32.4	46.7	34.8, 58.5	<0.001
Proportion of subjects with PASI ≤1†	57.1	14.3	42.9	31.4, 54.3	<0.001
DLQI total score 0 or 1†	66.7	25.7	41.0	28.8, 53.2	<0.001
Time-to-response assessments†	**Median time-to-response**		**Hazard ratio**	**95% CI**	***P*-value**
Time to PASI75, weeks†	4.1	16.4	5.0	3.4, 7.1	<0.0001
Time to PASI90, weeks†	7.4	24.4	6.3	4.0, 9.9	<0.0001

CI, confidence interval; CMH, Cochran–Mantel–Haenszel; DLQI, Dermatology Life Quality Index; FAE, fumaric acid esters; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment.
†Primary prespecified analysis of binary endpoints: Cochran–Mantel–Haenszel (CMH) analysis with non-responder imputation (NRI). ‡Primary endpoint. §Secondary endpoint. ¶Post hoc analysis. ††Analysed by Cox regression.

Safety

Most AEs in both treatment groups were mild to moderate in severity. There were no deaths, no serious infections and no major adverse cardiovascular events (MACE) in the trial, and the rate of SAEs in both treatment groups was low (Table 5). The rate of AEs was higher in the FAE group than in the brodalumab group [events per 100 exposure years (R) = 1195.8 vs. R = 616.4; Table 5]. The most common AEs in subjects treated with brodalumab were viral upper respiratory tract infections, headache and arthralgia. For subjects treated with FAE the most common AEs were diarrhoea, flushing, abdominal pain upper and viral upper respiratory tract infections. These are all known and expected AEs according to the product labels for brodalumab and FAE. Overall, the percentage and types of AEs reported in the brodalumab group in the CHANGE trial were similar to those reported in the phase 3 trials. No emergent safety signals were detected. AEs related to trial treatment and AEs leading to withdrawal from the trial occurred in more subjects treated with FAE than subjects treated with brodalumab (Table 5). The most common AEs in the FAE group leading to withdrawal were gastrointestinal disorders and lymphopenia; both are known and expected for FAE. The AEs leading to withdrawal in subjects treated with brodalumab were single events with no observable pattern. Oral candidiasis was reported in 5/104 subjects (4.8%) treated with brodalumab and in none treated with FAE. No cases led to discontinuation of brodalumab. Injection site reactions in the brodalumab group were infrequent (3/104 subjects, 2.9%), mild and resolved within 2–19 days. None led to withdrawal from the trial.

Serious adverse events (SAEs) were reported in 3/104 subjects (2.9%) treated with brodalumab (Table 5). One was hospitalized for a case of reactive gastropathy, one had a case of malignancy (pancreatic carcinoma metastatic), and one was hospitalized with a case of stasis dermatitis after trauma. Only the reactive gastropathy case was suspected to be related to the trial treatment. One SAE was reported in the FAE group. This was a case of Crohn's disease that led to hospitalization. It was suspected to be related to the trial treatment. No cases of inflammatory bowel disease were seen in any subjects treated with brodalumab.

There were no findings of SIB in any of the groups, based on the eC-SSRS assessment. PHQ-8 scores of 10–14 were recorded for 5/104 subjects (4.8%) in the brodalumab group, four of these at baseline, and 7/102 subjects (6.9%) in the FAE group, three of these at baseline. No PHQ-8 values ≥10 were reported after Week 2 in the brodalumab group and after Week 4 in the FAE group (Fig. 6). PHQ-8 scores ≥15 were recorded for 2/102 subjects (2.0%) in the FAE group; these subjects were withdrawn from the trial. No subjects in the brodalumab group had PHQ-8 scores ≥15 (Fig. 6).

Discussion

In this trial, we show that brodalumab had a superior efficacy profile compared to FAE (Fumaderm®; a mixture of dimethyl fumarate and monoethyl fumarate salts). Superiority was confirmed by sensitivity analyses performed on the primary endpoints and post hoc sensitivity analysis of the secondary endpoints, demonstrating robustness of the data, despite the high withdrawal rate in the FAE group. In treatment of psoriasis, rapid and complete skin clearance is valued highly by patients.[12] The median time to PASI75 was 4.1 weeks (compared to 16.4 weeks in the FAE group), which was equivalent to results in phase 3 trials[2] and thus supporting fast onset of action of brodalumab across trial settings (open-label and double-blind) and populations (systemic-naïve and systemic-experienced). Other direct comparisons between the CHANGE trial and the phase 3 trials are challenging, due to different trial designs. In the

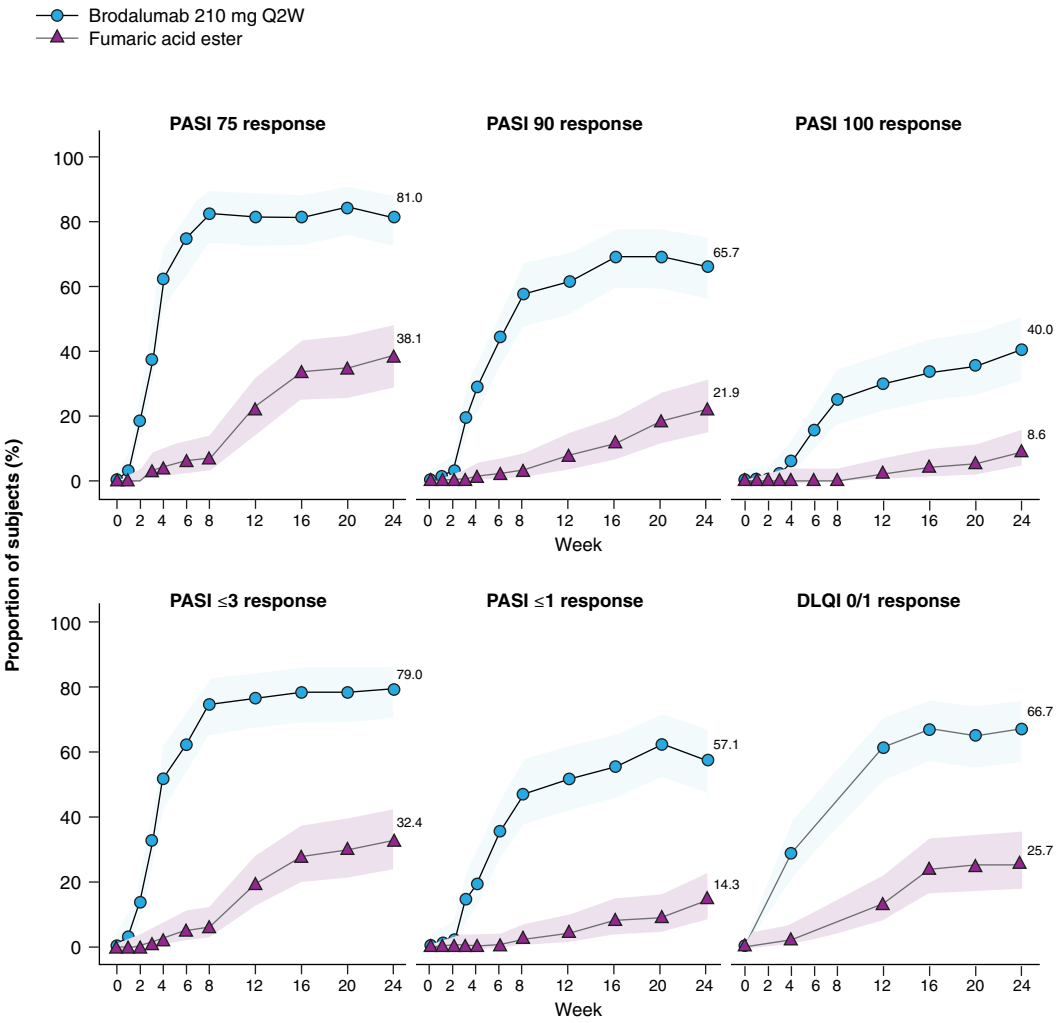

Figure 3 Binary efficacy assessments at Week 24. Treatment responses from baseline until Week 24 for binary efficacy assessments. Data were analysed using Cochran–Mantel–Haenszel analysis with non-responder imputation for missing data. Estimated mean values are shown ± 95% CI (grey area). Differences in response rates at Week 24 are all statistically significant ($P < 0.001$). CI, confidence interval; DLQI, Dermatology Life Quality Index; Q2W, every 2 weeks; PASI, Psoriasis Area and Severity Index.

CHANGE trial, brodalumab demonstrated fast onset of action (median 7.4 weeks to PASI90) and high rate of near-complete to complete skin clearance (sPGA 0/1 in 57.1%) in systemic-naïve subjects in an open-label phase 4 multi-centre setting, thus supporting these as a realistic treatment outcomes for a majority of patients when brodalumab is used as first-line systemic treatment.

Nail psoriasis affects up to 50–79% of patients with plaque psoriasis; it is difficult to treat with topical therapies alone, treatment response is often slow, and it can have great impact on patients' QoL.[13] In the brodalumab group, observed improvements in tNAPSI score of 38% and 76% were seen at weeks 12 and 24, respectively. This is in line with integrated data from the AMAGINE phase 3 trials with brodalumab; a mean improvement of 46.3% in tNAPSI score was seen after 12 weeks of treatment[14] and indicates that onset of effect of brodalumab in nail psoriasis occurs early. However, tNAPSI data from the CHANGE trial should be interpreted with caution, due to sparse data at Weeks 12 and 24.

Four recently published trials also reported H2H comparisons of FAE to a biologic for the treatment of moderate-to-severe psoriasis. These were secukinumab,[5] ixekizumab,[6] guselkumab[7] and risankizumab.[8] The trials all had similar designs (randomised, open-label, assessor-blinded, 24-week H2H trials),

Table 4 Continuous efficacy results

Continuousc assessment at Week 24	Estimated mean value		Estimated treatment difference	95% CI	*P*-value
	Brodalumab (*N* = 105)	FAE (*N* = 105)			
Primary analysis: MMRM†					
PASI score, absolute§	2.0	5.1	−3.1	−4.8, −1.3	<0.001
Post hoc analysis: LOCF‡					
PASI score, absolute§	2.8	8.2	−5.5	−7.5, −3.5	<0.001

Continuous assessments	Observed mean value (SD)		Number of subjects with data at Week 24	
	Brodalumab (*N* = 105)	FAE (*N* = 105)	Brodalumab	FAE
Data as observed at Week 24				
PASI score, absolute§	1.1 (1.7)	4.6 (7.0)	91	58
NAPSI score, absolute§	1.7 (2.4)	6.0 (4.5)	18	12
NAPSI score, % change from baseline§	−76% (34.2%)	−49% (33.6%)	18	12
Data as observed at Week 12				
tNAPSI score, absolute§	3.8 (3.7)	6.3 (5.0)	20	18
tNAPSI score, % change from baseline§	−38% (82.5%)	−31% (47.8%)	20	18

CI, confidence interval; FAE, fumaric acid esters; *N*, number of subjects; tNAPSI, target nail Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index. †Protocol prespecified primary analysis of continuous variables. ‡Post hoc sensitivity analyses of continuous variables using LOCF imputation for missing data. §Post hoc analysis.

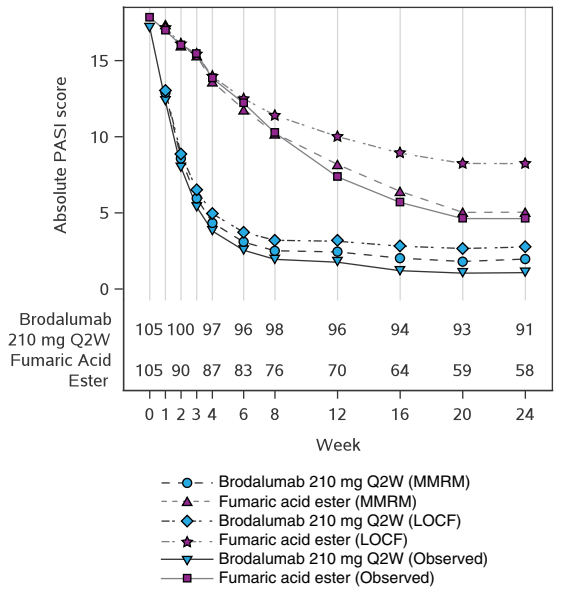

Figure 4 Mean absolute PASI score from baseline (Week 0) until Week 24. Numbers over the *x*-axis denote number of subjects with PASI data at a given week. Differences between brodalumab and fumaric acid ester in absolute PASI at Week 24 were statistically significant when either LOCF or MMRM were used for imputation of missing data ($P < 0.001$). MMRM was the protocol prespecified analysis, and LOCF was carried out as a post hoc sensitivity analysis and to facilitate comparison with other trials using LOCF for analysis of continuous variables. LOCF, last observation carried forward; MMRM, mixed model for repeated measurements; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks.

populations (systemic-naïve, moderate-to-severe disease) and outcomes (all confirmed superiority of a first-line biological treatment over FAE). In all trials, withdrawal rates in the FAE group were high, ranging from 22% to 55.7%[5–8]; withdrawal rate in CHANGE was 44.8%. However, there was a difference across these trials in how FAE was titrated. In the guselkumab,

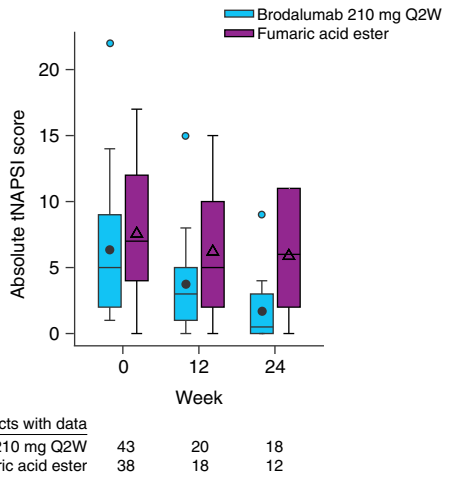

Figure 5 As-observed tNAPSI score at baseline (Week 0), Week 12 and Week 24. Lines in boxes indicate median, and symbols in boxes indicate mean. Boxes include first and third quartile values. Lower limit of whisker is interquartile range (IQR) minus 1.5 × IQR. Upper limit of whisker is IQR plus 1.5 × IQR. Data not included between the whiskers are extreme values. tNAPSI, target nail Nail Psoriasis Severity Index; Q2W, every 2 weeks.

Table 5 Adverse events

	Brodalumab			FAE		
Exposed subjects	**104**			**102**		
Exposure (subject years)	**56.8**			**33.5**		
	n	**%**	***R***	***n***	**%**	***R***
All AEs	91	87.5	616.4	96	94.1	1195.8
AEs related to trial treatment†	58	55.8	258.9	85	83.3	813.1
AEs leading to withdrawal from trial	6	5.8	15.9	27	26.5	107.6
Serious AEs (SAEs)	3	2.9	5.3	1	1.0	3.0
SAEs related to trial treatment†	1	1.0	1.8	1	1.0	3.0
SAEs leading to withdrawal from trial	2	1.9	3.5	1	1.0	3.0
Injection site reactions	3	2.9	5.3	0	0	NA
Major adverse cardiovascular events (MACE) ‡	0	0	NA	0	0	NA
Malignancies ‡	1§	1.0	1.8	0	0	NA
Serious infections ‡	0	0	NA	0	0	NA
Suicidal ideation and behaviour (SIB) ‡	0	0	NA	0	0	NA
Deaths	0	0	NA	0	0	NA
Most common AEs (reported in ≥5% of subjects) ¶						
Diarrhoea	4	3.8	7.0	59	57.8	230.2
Abdominal pain upper	2	1.9	3.5	28	27.5	128.5
Flushing	0	0	NA	29	28.4	119.6
Viral upper respiratory tract infection	35	33.7	72.2	21	20.6	71.7
Headache	13	12.5	47.6	12	11.8	56.8
Lymphopenia	2	1.9	5.3	14	13.7	41.9
Nausea	6	5.8	12.3	9	8.8	38.9
Abdominal pain	2	1.9	3.5	11	10.8	38.9
Fatigue	5	4.8	10.6	6	5.9	23.9
Depressive symptom	5	4.8	8.8	7	6.9	20.9
Arthralgia	9	8.7	17.6	4	3.9	12.0
Pruritus	6	5.8	10.6	2	2.0	6.0
Back pain	6	5.8	10.6	1	1.0	3.0
Oropharyngeal pain	6	5.8	10.6	1	1.0	3.0
Overdose††	8	7.7	14.1	0		
AEs of interest reported in <5% of subjects						
Oral candidiasis	5	4.8	12.3	0	0	NA
Influenza	2	1.9	3.5	0	0	NA
Crohn's disease	0	0	NA	1	1.0	3.0

AE, adverse event, FAE, fumaric acid esters; MACE, major adverse cardiovascular event; *n*, number of subjects; *R*, events per 100 exposure years; SAE, serious adverse event; SIB, suicidal ideation and behaviour.
†Possibly or probably related to the trial treatment in the opinion of the investigator. ‡Protocol-defined adverse events of special interest. §Pancreatic carcinoma metastatic, not related to trial treatment. ¶Reported as Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 preferred term. ††An overdose was defined as a subject receiving a dose in excess of that specified in the protocol.

secukinumab and risankizumab H2H trials, FAE titration was continued until at least PASI75[15] or PASI90[16,17] was reached. In the CHANGE trial, investigators were instructed to titrate FAE to best possible effect according to the product label throughout the trial and not stop when PASI75 or PASI90 was reached. The PASI75 response rate in the FAE groups ranged from 22.2% to 38.1% at Week 24[5–8]; response rate in CHANGE was 38.1%. The PASI90 and PASI100 response rates in the FAE groups at Week 24 ranged from 9.3% to 21.9% and 3.2% to 8.6%, respectively[15–17]; response rates in CHANGE were 21.9% and 8.6%, respectively. The difference in titration may explain the difference in FAE response rates. Considering this, the relative differences in response rates between FAE and the biological comparators are likely not directly comparable.

Depression is a well-known co-morbidity of chronic inflammatory skin diseases, and prevalence is up to 20% in psoriasis patients.[18] Two subjects had moderate-to-severe depression (PHQ-8 score ≥15) during the trial; these were withdrawn in accordance with the protocol. Both were in the FAE group. Few subjects reported moderate depression (PHQ-8 of 10–14), and none after Week 2 in the brodalumab group and Week 4 in the FAE group. This could potentially indicate that relief from

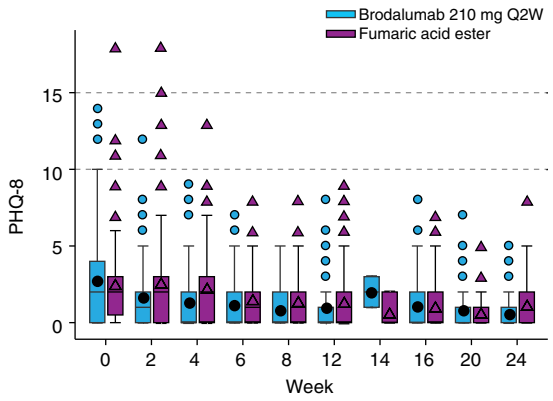

Figure 6 As-observed PHQ-8 scores from baseline to Week 24. Lines in boxes indicate median, and symbols in boxes indicate mean. Boxes include first and third quartile values. Lower limit of whisker is interquartile range (IQR) minus 1.5 × IQR. Upper limit of whisker is IQR plus 1.5 × IQR. Data not included between the whiskers are extreme values. Q2W, every 2 weeks; PHQ-8, Patient Health Questionnaire 8.

psoriasis symptoms may have a beneficial effect on patients' mood, which is in line with a recent registry study showing that treatment with biologics was associated with lower incidence of depressive symptoms.[19] However, the data should be interpreted with caution due to the low number of subjects and the descriptive nature of the data.

No new or unexpected safety signals were observed for brodalumab or FAE in the CHANGE trial.

A limitation of this trial was the open-label design, which could have induced bias in the reporting of PROs and AEs. However, it could also be argued that open-label administration is closer to the real-world clinical setting of psoriasis treatment. Another limitation was the high withdrawal rate in the FAE group (44.8%). This did not affect the power of the trial, as a withdrawal rate of 50% was assumed in the sample size calculation. However, it contributed to the variation observed in the results, depending on which method was used to impute missing data. This variation was more pronounced in the FAE group, as the withdrawal rate was higher; 44.8% vs. 13.3% in the brodalumab group. This serves to highlight the importance of looking at clinical data through the lens of the applied statistical method, especially when comparing data across trials, as also pointed out in a recent post hoc analysis of data from two phase III trials in psoriasis.[20] The prespecified imputation method for continuous variables in this trial was MMRM, where other recent H2H trials with biologics and FAE in psoriasis used LOCF.[6–8] Given the variability in the estimated treatment response that arose from using different imputation methods, care should be taken when comparing results across these trials.

Data have previously shown that the efficacy of FAE may increase beyond 24 weeks,[21] so the relatively short duration of the trial could also be a limitation. However, the high withdrawal rate of subjects randomized to FAE would likely lead to even more uncertainty of results beyond Week 24 due to the need for imputation of missing data. In addition, 24 weeks is an acceptable length of treatment in a trial with a chronic disease, according to the German Institute for Quality and Efficiency in Healthcare.[22]

In conclusion, the CHANGE trial demonstrated the superiority of brodalumab over the conventional systemic therapy FAE after 24 weeks of treatment in terms of clinical efficacy and QoL. Brodalumab also demonstrated a better safety and tolerability profile. The results from the CHANGE trial indicate that brodalumab as first-line treatment in systemic-naïve patients with moderate-to-severe psoriasis can result in fast onset of action and a PASI75 or PASI90 response in most patients, with few experiencing side-effects leading to treatment discontinuation. Data from this and other similar trials could potentially be used to update systemic treatment algorithms and guidelines for systemic-naïve psoriasis patients.

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References

1 Papp KA, Reich K, Paul C *et al.* A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2016; **175**: 273–286.
2 Lebwohl M, Strober B, Menter A *et al.* Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015; **373**: 1318–1328.
3 Mrowietz U, Morrison PJ, Suhrkamp I, Kumanova M, Clement B. The pharmacokinetics of fumaric acid esters reveal their in vivo effects. *Trends Pharmacol Sci* 2018; **39**: 1–12.
4 Nast A, Amelunxen L, Augustin M *et al.* S3 Guideline for the treatment of psoriasis vulgaris, update - Short version part 1 - Systemic treatment. *J Dtsch Dermatol Ges* 2018; **16**: 645–669.
5 Sticherling M, Mrowietz U, Augustin M *et al.* Secukinumab is superior to fumaric acid esters in treating patients with moderate-to-severe plaque

psoriasis who are naive to systemic treatments: results from the randomized controlled PRIME trial. *Br J Dermatol* 2017; **177**: 1024–1032.
6 Reich K, Augustin M, Thaci D *et al*. A 24-week multicentre, randomized, open-label, parallel-group study comparing the efficacy and safety of ixekizumab vs. fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis naive to systemic treatment. *Br J Dermatol* 2020; **182**: 869–879.
7 Thaci D, Pinter A, Sebastian M *et al*. Guselkumab is superior to fumaric acid esters in patients with moderate-to-severe plaque psoriasis who are naive to systemic treatment: results from a randomized, active-comparator-controlled phase IIIb trial (POLARIS). *Br J Dermatol* 2020; **183**: 265–275.
8 AbbVie. AbbVie. A study to assess the efficacy of risankizumab compared to FUMADERM® in subjects with moderate to severe plaque psoriasis who are naïve to and candidates for systemic therapy. identifier NCT03255382; 2020. URL Clinicaltrials.govhttps://clinicaltrials.gov/ct2/show/study/NCT03255382 (last accessed 03 March 2020).
9 G-BA. Scientific Advice (2016-B-165) of the Gemeinsamer Bundesausschuss (G-BA) according to § 8 Abs.1 AM-NutzenV; 2017. *Internal reference, available on request*.
10 Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003; **49**: 206–212.
11 Mahil SK, Wilson N, Dand N *et al*. Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR). *Br J Dermatol* 2020; **182**: 1158–1166.
12 Maul JT, Navarini AA, Sommer R *et al*. Gender and age significantly determine patient needs and treatment goals in psoriasis - a lesson for practice. *J Eur Acad Dermatol Venereol* 2019; **33**: 700–708.
13 Bardazzi F, Starace M, Bruni F, Magnano M, Piraccini BM, Alessandrini A. Nail psoriasis: an updated review and expert opinion on available treatments, including biologics. *Acta Derm Venereol* 2019; **99**: 516–523.
14 Elewski B, Riche P, Han G, Scher RK, Jacobson A. Improvement of nail psoriasis with brodalumab in phase 3 trials. *J Am Acad Dermatol* 2017; **76**: AB410.
15 IQWiG. Secukinumab (plaque psoriasis) - Benefit assessment according to §35a Social Code Book V (new scientific findings); 2017.
16 IQWiG. Guselkumab (plaque psoriasis) - Benefit assessment according to §35a Social Code Book V; 2018.
17 IQWiG. Risankizumab (plaque psoriasis) - Nutzenbewertung gemäß § 35a SGB V; 2019.
18 Cai Q, Teeple A, Wu B, Muser E. Prevalence and economic burden of comorbid anxiety and depression among patients with moderate-to-severe psoriasis. *J Med Econ* 2019; **22**: 1290–1297.
19 Strober B, Gooderham M, de Jong E *et al*. Depressive symptoms, depression, and the effect of biologic therapy among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Am Acad Dermatol* 2018; **78**: 70–80.
20 Langley RGB, Reich K, Papavassilis C, Fox T, Gong Y, Gu TA. Methods for imputing missing efficacy data in clinical trials of biologic psoriasis therapies: implications for interpretations of trial results. *J Drugs Dermatol* 2017; **16**: 734–741.
21 Altmeyer P, Hartwig R, Matthes U. Das Wirkungs- und Sicherheitsprofil von Fumarsäureestern in der oralen Langzeittherapie bei schwerer therapieresistenter Psoriasis vulgaris. Eine Untersuchung an 83 Patienten. *Der Hautarzt* 1996; **47**: 190–196.
22 IQWiG. Brodalumab (plaque psoriasis) – Benefit assessment according to §35a Social Code Book V; 2017.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sensitivity analyses of primary endpoints.
Table S2. Supplementary continuous efficacy results.