Clinical trial results:
A phase 4 trial comparing the efficacy of subcutaneous injections of brodalumab to oral administrations of fumaric acid esters in adults with moderate to severe plaque psoriasis

Summary

EudraCT number	2016-003867-21
Trial protocol	DE
Global end of trial date	21 March 2019

Results information

Result version number	v1 (current)
This version publication date	13 February 2020
First version publication date	13 February 2020

Trial information

Trial identification

Sponsor protocol code	LP0160-1327

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03331835
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com
Scientific contact	Clinical Disclosure, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2019
Global end of trial reached?	Yes
Global end of trial date	21 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of subcutaneous injections of brodalumab to oral administration of fumaric acid esters in subjects with moderate to severe plaque psoriasis who are naive to systemic treatment.

Protection of trial subjects:

This clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly, 1964, and subsequent amendments.
All subjects or their legally acceptable representative received written and verbal information concerning the clinical trial.
Subjects or their legally acceptable representative were asked to consent that their personal data were recorded, collected, processed and could be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection.

Background therapy: -

Evidence for comparator:

An oral preparation containing fumaric acid esters (dimethyl fumarate and monoethyl fumarate salts; Fumaderm®) was selected as comparator, because it is a well-established and widely used systemic treatment in Germany for patients with moderate to severe plaque psoriasis in whom topical therapy is not effective (Nast et al. J Dtsch Dermatol Ges. 2018;165]:645-669). Fumaric acid esters were recommended in 2017 as appropriate comparator for this patient population by the Federal Joint Committee (G-BA), a German decision-making body (Scientific Advice [2016-B-165] of the Gemeinsamer Bundesausschuss (G-BA) according to § 8 Abs.1 AM-NutzenV. 2017).

Actual start date of recruitment	01 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 210
Worldwide total number of subjects	210
EEA total number of subjects	210

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	193
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Number of subjects screened: 325
Screening failures: 101
Withdrawn before randomisation: 14

Period 1

Period 1 title	Open-label treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The risk of bias related to open-label treatment was mitigated by blinded investigator assessments and detailed precautions were taken to avoid unblinding assessors. Due to potential dose adjustments needed for subjects randomised to fumaric acid esters, the investigator and subject needed to know the treatment allocated. The sponsor was also blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brodalumab

Arm description:

Brodalumab 210 mg s.c. injection Q2W

Arm type	Experimental
Investigational medicinal product name	Brodalumab
Investigational medicinal product code	
Other name	Kyntheum (R)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage: 210 mg in 1.5 mL solution for subcutaneous injection (140 mg/mL). Weekly administration for the first 3 weeks (Weeks 0, 1, and 2) followed by administration every 2 weeks (Q2W) up to Week 24.

Arm title	Fumaric acid esters

Arm description:

Oral fumaric acid esters up to 240 mg 3 times daily (TID)

Arm type	Active comparator
Investigational medicinal product name	fumaric acid esters
Investigational medicinal product code	
Other name	Fumaderm (R), Fumaderm (R) initial
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administration by participant 3 times daily in doses ranging from 30 to 240 mg dimethyl fumarate per oral administration.

Number of subjects in period 1	Brodalumab	Fumaric acid esters
Started	105	105
Completed	91	58
Not completed	14	47
Consent withdrawn by subject	1	8
Adverse event, non-fatal	7	28
Other reason	5	5
Lost to follow-up	-	2
Lack of efficacy	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Brodalumab
Reporting group description:	
Brodalumab 210 mg s.c. injection Q2W	
Reporting group title	Fumaric acid esters
Reporting group description:	
Oral fumaric acid esters up to 240 mg 3 times daily (TID)	

Reporting group values	Brodalumab	Fumaric acid esters	Total
Number of subjects	105	105	210
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	96	97	193
From 65-84 years	9	8	17
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44.0	43.9	
standard deviation	± 14.3	± 13.9	-
Gender categorical			
Units: Subjects			
Female	32	33	65
Male	73	72	145
Race			
Units: Subjects			
Asian	1	0	1
White	104	105	209
Ethnicity			
Units: Subjects			
Not Hispanic Or Latino	100	103	203
Not reported	1	1	2
Unknown	4	1	5
Height			
Units: cm			
arithmetic mean	175	176	
standard deviation	± 9.6	± 9.8	-
Weight			
Units: kg			
arithmetic mean	87.8	86.6	

standard deviation	± 20.4	± 21.1	-
Weight in weight group <100 kg			
Units: kg			
arithmetic mean	78.4	77.2	
standard deviation	± 11.9	± 12.8	-
Body Mass Index			
Units: kg/m2			
arithmetic mean	28.5	28.0	
standard deviation	± 5.7	± 6.0	-
Duration of psoriasis			
Units: years			
arithmetic mean	14.3	13.2	
standard deviation	± 11.5	± 11.7	-
PASI score			
Units: score on a scale			
arithmetic mean	17.2	17.8	
standard deviation	± 5.9	± 6.7	-
sPGA score			
Units: score on a scale			
arithmetic mean	3.5	3.5	
standard deviation	± 0.6	± 0.7	-
BSA score			
Units: score on a scale			
arithmetic mean	24.8	25.5	
standard deviation	± 15.2	± 14.9	-
NAPSI score			
NAPSI score was only collected for subjects with nail involvement at baseline. The number of subjects with a NAPSI score at baseline were n=43 in the brodalumab arm and 38 in the fumaric acid esters arm.			
Units: score on a scale			
arithmetic mean	6.4	7.7	
standard deviation	± 4.4	± 4.9	-
DLQI score			
Units: score on a scale			
arithmetic mean	18.8	18.5	
standard deviation	± 5.2	± 4.9	-
PSI score			
Due to operational difficulties with the ePRO diaries handed our to subjects, baseline PSI data is missing for some subjects. PSI data at baseline was collected from n=83 in the brodalumab arm and n=78 in the fumaric acid esters arm.			
Units: score on a scale			
arithmetic mean	14.8	17.9	
standard deviation	± 5.4	± 5.3	-

End points

End points reporting groups	
Reporting group title	Brodalumab
Reporting group description: Brodalumab 210 mg s.c. injection Q2W	
Reporting group title	Fumaric acid esters
Reporting group description: Oral fumaric acid esters up to 240 mg 3 times daily (TID)	

Primary: Having Least 75% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 75 Response) From Baseline at Week 24

End point title	Having Least 75% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 75 Response) From Baseline at Week 24
End point description: Co-primary endpoint	
End point type	Primary
End point timeframe: Week 24	

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: percent				
number (not applicable)	81.0	38.10		

Statistical analyses

Statistical analysis title	Analysis of co-primary endpoint PASI75

Statistical analysis description:

The difference in response rate between treatment groups was analysed using the Cochran-Mantel-Haenszel test with stratification by weight group (≥100 kg or <100 kg). The null hypotheses of no difference in response rates between brodalumab and fumaric acid esters was tested against the two-sided alternative that there was a difference on a 5% level. Subjects who drop-out of the trial before Week 24 (end of treatment visit) were regarded as non-responders.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	42.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	30.93
upper limit	54.79

Primary: Static Physician’s Global Assessment (sPGA) scale score of 0 or 1 at Week 24

End point title	Static Physician’s Global Assessment (sPGA) scale score of 0 or 1 at Week 24
End point description: Co-primary endpoint	
End point type	Primary
End point timeframe: 24 weeks	

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: percent				
number (not applicable)	64.8	20.0		

Statistical analyses

Statistical analysis title	Analysis of co-primary endpoint sPGA 0 or 1

Statistical analysis description:

The difference in response rate between treatment groups was analysed using the Cochran-Mantel-Haenszel test with stratification by weight group (≥100 kg or <100 kg). The null hypotheses of no difference in response rates between brodalumab and fumaric acid esters was tested against the two-sided alternative that there was a difference on a 5% level. Subjects who drop-out of the trial before Week 24 (end of treatment visit) were regarded as non-responders.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	44.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.81
upper limit	56.71

Secondary: Having Least 90% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 90 Response) From Baseline at Week 24

End point title	Having Least 90% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 90 Response) From Baseline at Week 24

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: percent				
number (not applicable)	65.7	21.9		

Statistical analyses

Statistical analysis title	Analysis of secondary endpoint PASI90

Statistical analysis description:

The difference in response rate between treatment groups was analysed using the Cochran-Mantel-Haenszel test with stratification by weight group (≥100 kg or <100 kg). The null hypotheses of no difference in response rates between brodalumab and fumaric acid esters was tested against the two-sided alternative that there was a difference on a 5% level. Subjects who drop-out of the trial before Week 24 (end of treatment visit) were regarded as non-responders.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	43.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.78
upper limit	55.84

Secondary: Having 100% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 100 Response) From Baseline at Week 24

End point title	Having 100% Lower Psoriasis Area and Severity Index (PASI) Score Relative to Baseline (PASI 100 Response) From Baseline at Week 24

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: percent				
number (not applicable)	40.0	8.6		

Statistical analyses

Statistical analysis title	Analysis of secondary endpoint PASI100

Statistical analysis description:

The difference in response rate between treatment groups was analysed using the Cochran-Mantel-Haenszel test with stratification by weight group (≥100 kg or <100 kg). The null hypotheses of no difference in response rates between brodalumab and fumaric acid esters was tested against the two-sided alternative that there was a difference on a 5% level. Subjects who drop-out of the trial before Week 24 (end of treatment visit) were regarded as non-responders.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	31.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.76
upper limit	42.1

Secondary: Change from baseline at Week 24 in PASI score

End point title	Change from baseline at Week 24 in PASI score

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	96		
Units: score on a scale				
arithmetic mean (standard error)	-15.69 (± 0.59)	-12.62 (± 0.67)		

Statistical analyses

Statistical analysis title	Mean change from baseline in PASI score

Statistical analysis description:

The endpoint was analysed by using mixed model for repeated measures (MMRM) model including treatment group, week, interaction between treatment and time, baseline value, and baseline weight group as fixed factors. Within subject covariance was estimated by an unstructured covariance matrix.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.83
upper limit	-1.33

Secondary: PASI improvement (%) from baseline at Week 24

End point title	PASI improvement (%) from baseline at Week 24

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	96		
Units: percentage				
arithmetic mean (standard error)	-90.03 (± 2.25)	-73.67 (± 2.63)		

Statistical analyses

Statistical analysis title	PASI improvement (%) from baseline to Week 24

Statistical analysis description:

The endpoint was analysed using mixed model for repeated measures (MMRM) model including treatment group, week, interaction between treatment and time, baseline value, and baseline weight group as fixed factors. Within subject covariance was estimated by an unstructured covariance matrix. Treatment groups were defined as randomised treatment.

Number of randomised and analysed paticipants differs, as those with missing data in all visits for a given endpoint are not included in the analysis.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-16.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.03
upper limit	-9.68

Secondary: Change from baseline at Week 24 in affected BSA

End point title	Change from baseline at Week 24 in affected BSA

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: percent				
number (not applicable)	-20.82	-11.91		

Statistical analyses

Statistical analysis title	Change from baseline at Week 24 in affected BSA

Statistical analysis description:

The endpoint was analysed using mixed model for repeated measures (MMRM) model including treatment group, week, interaction between treatment and time, baseline value, and baseline weight group as fixed factors. Within subject covariance was estimated by an unstructured covariance matrix. Treatment groups were defined as randomised treatment.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	-4.81

Secondary: Psoriasis Symptom Inventory (PSI) responder at Week 24

End point title	Psoriasis Symptom Inventory (PSI) responder at Week 24

End point description:

A PSI responder is defined as having a total score ≤8 and no item score >1. No statistical analysis of this data was performed due to missing data at both baseline and Week 24. This was due to operational challenges with the eDiaries handed out to subjects.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[1]	15[2]		
Units: subjects	15	13		

Notes:

[1] - Less than 105 subjects had data at Week 24.

[2] - Less than 105 subjects had data at Week 24.

Statistical analyses

No statistical analyses for this end point

Secondary: PSI total score of 0 at Week 24

End point title	PSI total score of 0 at Week 24

End point description:

No statistical analysis of this data was performed due to missing data at baseline and Week 24. This was due to operational challenges with the eDiary devices handed out to subjects.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[3]	15[4]		
Units: subjects	5	3		

Notes:

[3] - Less than 105 subjects had data at Week 24.

[4] - Less than 105 subjects had data at Week 24.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of symptom-free days from randomisation to Week 24

End point title	Number of symptom-free days from randomisation to Week 24

End point description:

A symptom-free day was defined as a total PSI of 0 on that day. No statistical analysis of this data was performed due to missing data at baseline and Week 24. This was due to operational challenges with the eDiary devices handed out to subjects.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[5]	33[6]		
Units: days				
arithmetic mean (standard deviation)	0.44 (± 0.8)	0.42 (± 1.3)		

Notes:

[5] - Less than 105 subjects had data at Week 24

[6] - Less than 105 subjects had data at Week 24

Statistical analyses

No statistical analyses for this end point

Secondary: Burden of symptoms shown as area under curve (AUC) of PSI total score

End point title	Burden of symptoms shown as area under curve (AUC) of PSI total score

End point description:

Burden of symptoms was assessed as the normalised AUC of PSI total score from baseline to the last available assessment. The AUC for the PSI total score was calculated for each subject using the standard trapezoidal rule. The AUC was then normalised by dividing it with the time from baseline to the last available assessment of the PSI total score.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[7]	78[8]		
Units: area under curve				
arithmetic mean (standard error)	6.00 (± 0.54)	10.92 (± 0.55)		

Notes:

[7] - Not all 105 subjects had data available for analysis for this endpoint

[8] - Not all 105 subjects had data available for analysis for this endpoint

Statistical analyses

Statistical analysis title	AUC of PSI total score

Statistical analysis description:

The AUC was analysed using an analysis of covariance (ANCOVA) with treatment group, baseline weight group, and the baseline PSI total score as explanatory variables. Treatment groups are defined as randomised treatment.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-4.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.31
upper limit	-3.53

Secondary: Change from baseline at Week 24 DLQI total score

End point title	Change from baseline at Week 24 DLQI total score

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	86		
Units: score on a scale				
arithmetic mean (standard error)	-16.67 (± 0.61)	-14.10 (± 0.70)		

Statistical analyses

Statistical analysis title	Change from baseline in DLQI total score at Week24

Statistical analysis description:

The endpoint was analysed by using mixed model for repeated measures (MMRM) model including treatment group, week, interaction between treatment and time, baseline value, and baseline weight group as fixed factors. Within subject covariance was estimated by an unstructured covariance matrix.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.32
upper limit	-0.82

Secondary: DLQI total score of 0 or 1 at Week 24

End point title	DLQI total score of 0 or 1 at Week 24

End point description:

End point type	Secondary

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	105		
Units: subjects	70	27		

Statistical analyses

Statistical analysis title	DLQI total score of 0 or 1 at Week 24

Statistical analysis description:

Estimated risk difference, 95% CI and p-value were derived from CMH analysis stratified by weight group at baseline (≤100 kg, > 100 kg). Non-responder imputation (NRI) was used to impute missing data. Treatment groups were defined as randomised treatment.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	40.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.75
upper limit	53.16

Other pre-specified: Change from baseline at Week 24 in NAPSI total score

End point title	Change from baseline at Week 24 in NAPSI total score

End point description:

End point type	Other pre-specified

End point timeframe:

24 weeks

End point values	Brodalumab	Fumaric acid esters		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[9]	38[10]		
Units: score on a scale				
arithmetic mean (standard error)	2.97 (± 0.54)	-1.26 (± 0.57)		

Notes:

[9] - Only subjects with nail psoriasis at baseline were included in this end point.

[10] - Only subjects with nail psoriasis at baseline were included in this end point.

Statistical analyses

Statistical analysis title	Change from baseline in NAPSI score at Week 24

Statistical analysis description:

The endpoint was analysed by using mixed model for repeated measures (MMRM) model including treatment group, week, interaction between treatment and time, baseline value, and baseline weight group as fixed factors. Within subject covariance was estimated by an unstructured covariance matrix. Treatment groups were defined as randomised treatment.

Comparison groups	Brodalumab v Fumaric acid esters
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	-0.19

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Fumaric Acid Ester
Reporting group description: -	
Reporting group title	Brodalumab 210 mg Q2W
Reporting group description: -	

Serious adverse events	Fumaric Acid Ester	Brodalumab 210 mg Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)	3 / 104 (2.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 102 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Crohn's disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 102 (0.98%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive gastropathy			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 102 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 102 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Fumaric Acid Ester	Brodalumab 210 mg Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 102 (94.12%)	91 / 104 (87.50%)	
Injury, poisoning and procedural complications			
Overdose			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 102 (0.00%)	8 / 104 (7.69%)	
occurrences (all)	0	8	
Vascular disorders			
Flushing			
alternative assessment type: Non-systematic			
subjects affected / exposed	29 / 102 (28.43%)	0 / 104 (0.00%)	
occurrences (all)	40	0	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 102 (11.76%)	13 / 104 (12.50%)	
occurrences (all)	19	27	
Blood and lymphatic system disorders			
Lymphopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 102 (13.73%)	2 / 104 (1.92%)	
occurrences (all)	14	3	

General disorders and administration site conditions			
Fatigue			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 102 (5.88%)	5 / 104 (4.81%)	
occurrences (all)	8	6	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 102 (10.78%)	2 / 104 (1.92%)	
occurrences (all)	13	2	
Abdominal pain upper			
alternative assessment type: Non-systematic			
subjects affected / exposed	28 / 102 (27.45%)	2 / 104 (1.92%)	
occurrences (all)	43	2	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	59 / 102 (57.84%)	4 / 104 (3.85%)	
occurrences (all)	77	4	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 102 (8.82%)	6 / 104 (5.77%)	
occurrences (all)	13	7	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 102 (0.98%)	6 / 104 (5.77%)	
occurrences (all)	1	6	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 102 (1.96%)	6 / 104 (5.77%)	
occurrences (all)	2	6	
Psychiatric disorders			
Depressive symptom			
alternative assessment type: Non-systematic			

subjects affected / exposed	7 / 102 (6.86%)	5 / 104 (4.81%)	
occurrences (all)	7	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 102 (3.92%)	9 / 104 (8.65%)	
occurrences (all)	4	10	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 102 (0.98%)	6 / 104 (5.77%)	
occurrences (all)	1	6	
Infections and infestations			
Viral upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 102 (20.59%)	35 / 104 (33.65%)	
occurrences (all)	24	41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2017	The reason for the amendment is to implement requirements from the health authorities in Germany.
17 August 2018	The reason for Amendment 2 is to clarify that exclusion criteria related to the PROs eC-SSRS and PHQ-8 pertain to both the screening and the baseline visit. Also, the wording for the eC-SSRS criteria, and the described assessment hereof, has been updated to reflect the report from the eC-SSRS. The wording in version 3.0 of the protocol was based on the paper version of the C-SSRS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported