Clinical trial results:
Multicenter, Double-Blind, Randomized, Active- and Placebo Controlled Study to Evaluate Safety, Tolerability, and Efficacy of Ixekizumab in Patients from 6 to Less than 18 Years of Age with Moderate-to-Severe Plaque Psoriasis.

Summary

EudraCT number	2016-003331-38
Trial protocol	NL DE ES PL HU CZ FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	22 February 2020
First version publication date	22 February 2020

Trial information

Trial identification

Sponsor protocol code	I1F-MC-RHCD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03073200
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16367

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001050-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	07 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of ixekizumab in pediatric participants with moderate-to-severe plaque psoriasis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Puerto Rico: 8
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	United States: 64
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Czech Republic: 12
Worldwide total number of subjects	201
EEA total number of subjects	87

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	49
Adolescents (12-17 years)	152
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Open-Label Etanercept group occurred only in Etanercept approved countries.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo for Ixekizumab by subcutaneous injection.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received matching placebo for Ixekizumab by subcutaneous injection.

Arm title	Ixekizumab

Arm description:

Participants with >50kg received 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks (Q4W) from week 4 to 8 followed by 80mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with 25 to 50kg received 80mg Ixekizumab at week 0 followed by 40mg Ixekizumab Q4W from week 4 to 8 followed by 40mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with >25kg received 40mg Ixekizumab at week 0 followed by 20mg Ixekizumab Q4W from week 4 to 8 followed by 20mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Arm type	Experimental
Investigational medicinal product name	Ixekizumab
Investigational medicinal product code	
Other name	LY2439821
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants with >50kg received 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks (Q4W) from week 4 to 8 followed by 80mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with 25 to 50kg received 80mg Ixekizumab at week 0 followed by 40mg Ixekizumab Q4W from week 4 to 8 followed by 40mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with >25kg received 40mg Ixekizumab at week 0 followed by 20mg Ixekizumab Q4W from week 4 to 8 followed by 20mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Arm title	Open-Label Etanercept

Arm description:

Participants received 0.8mg/kg Etanercept not exceeding 50mg per dose every week from week 0 to week 11 by subcutaneous injection.

Arm type	Active comparator
Investigational medicinal product name	Etanerccept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe, Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 0.8mg/kg Etanercept not exceeding 50mg per dose every week from week 0 to week 11 by subcutaneous injection.

Number of subjects in period 1	Placebo	Ixekizumab	Open-Label Etanercept
Started	56	115	30
Subjects (Etanercept approved countries)	19	38	30
Completed	1	0	0
Not completed	55	115	30
Consent withdrawn by subject	3	3	-
Site closed by sponsor	-	-	1
Adverse event, non-fatal	-	2	-
Withdrawal by parent or guardian	-	1	1
Participant has Crohns disease	-	1	-
Continuing treatment (Ongoing)	48	106	28
Lost to follow-up	1	2	-
Lack of efficacy	1	-	-
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo for Ixekizumab by subcutaneous injection.	
Reporting group title	Ixekizumab
Reporting group description:	
Participants with >50kg received 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks (Q4W) from week 4 to 8 followed by 80mg ixekizumab and placebo injection at week 12 by subcutaneous injection. Participants with 25 to 50kg received 80mg Ixekizumab at week 0 followed by 40mg Ixekizumab Q4W from week 4 to 8 followed by 40mg ixekizumab and placebo injection at week 12 by subcutaneous injection. Participants with >25kg received 40mg Ixekizumab at week 0 followed by 20mg Ixekizumab Q4W from week 4 to 8 followed by 20mg ixekizumab and placebo injection at week 12 by subcutaneous injection.	
Reporting group title	Open-Label Etanercept
Reporting group description:	
Participants received 0.8mg/kg Etanercept not exceeding 50mg per dose every week from week 0 to week 11 by subcutaneous injection.	

Reporting group values	Placebo	Ixekizumab	Open-Label Etanercept
Number of subjects	56	115	30
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	13.1	13.7	13.7
standard deviation	± 2.79	± 3.14	± 2.95
Gender categorical Units: Subjects			
Female	36	63	18
Male	20	52	12
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	30	7
Not Hispanic or Latino	42	82	23
Unknown or Not Reported	3	3	0
Race (NIH/OMB)			

Units: Subjects			
American Indian or Alaska Native	0	2	1
Asian	2	4	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	0
White	45	95	25
More than one race	3	10	3
Unknown or Not Reported	3	1	1
Region of Enrollment			
Units: Subjects			
Puerto Rico	3	5	0
Argentina	3	7	3
Hungary	6	13	2
United States	22	42	0
Czechia	2	6	4
Spain	5	4	3
Russia	4	7	4
Canada	1	6	0
Netherlands	0	1	0
Poland	5	12	8
Mexico	1	4	2
France	1	1	1
Germany	3	7	3
Psoriasis Area Severity Index (PASI)			
PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe Fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement). Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).			
Units: Score on a scale			
arithmetic mean	19.73	19.75	24.78
standard deviation	± 8.010	± 7.509	± 7.448
Static Physician Global Assessment (sPGA)			
Static Physician Global Assessment (sPGA): The physician's global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).			
Units: Score on a scale			
arithmetic mean	3.5	3.6	4.1
standard deviation	± 0.63	± 0.61	± 0.31

Reporting group values	Total		
Number of subjects	201		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	117		
Male	84		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	48		
Not Hispanic or Latino	147		
Unknown or Not Reported	6		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	3		
Asian	6		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	6		
White	165		
More than one race	16		
Unknown or Not Reported	5		
Region of Enrollment			
Units: Subjects			
Puerto Rico	8		
Argentina	13		
Hungary	21		
United States	64		
Czechia	12		
Spain	12		
Russia	15		
Canada	7		
Netherlands	1		
Poland	25		
Mexico	7		
France	3		
Germany	13		
Psoriasis Area Severity Index (PASI)			
PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe Fraction of total body surface area affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement). Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).			
Units: Score on a scale			
arithmetic mean			

standard deviation	-		
Static Physician Global Assessment (sPGA)			
Static Physician Global Assessment (sPGA): The physician's global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).			
Units: Score on a scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo for Ixekizumab by subcutaneous injection.

Reporting group title	Ixekizumab

Reporting group description:

Participants with >50kg received 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks (Q4W) from week 4 to 8 followed by 80mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with 25 to 50kg received 80mg Ixekizumab at week 0 followed by 40mg Ixekizumab Q4W from week 4 to 8 followed by 40mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Participants with >25kg received 40mg Ixekizumab at week 0 followed by 20mg Ixekizumab Q4W from week 4 to 8 followed by 20mg ixekizumab and placebo injection at week 12 by subcutaneous injection.

Reporting group title	Open-Label Etanercept

Reporting group description:

Participants received 0.8mg/kg Etanercept not exceeding 50mg per dose every week from week 0 to week 11 by subcutaneous injection.

Primary: Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75) (Placebo and Ixekizumab)

End point title	Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75) (Placebo and Ixekizumab)[1]

End point description:

PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
Fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement): 0 = 0% (clear), 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to 90%, 6 = 90% to 100%.
Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).
APD: All randomized Pts in placebo and Ixekizumab. Missing values were imputed by Nonresponder imputation.
Pts who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Primary

End point timeframe:

Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	25.0	88.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	63.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	51
upper limit	76.4

Primary: Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1) (Placebo and Ixekizumab)

End point title	Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1) (Placebo and Ixekizumab)[2]

End point description:

Static Physician Global Assessment (sPGA): The physician’s global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).
An sPGA assessed as either 0 or 1 represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.

Analysis Population Description (APD): All randomized participants in placebo and Ixekizumab arms.
Missing values were imputed by Nonresponder imputation (NRI).
Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Primary

End point timeframe:

Week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	10.7	80.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	70.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	59.3
upper limit	81

Secondary: Percentage of Participants with a ≥90% Improvement in Psoriasis Area and Severity Index (PASI 90)

End point title	Percentage of Participants with a ≥90% Improvement in Psoriasis Area and Severity Index (PASI 90)[3]

End point description:

PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe Fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement): 0 = 0% (clear), 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to 90%, 6 = 90% to 100%.Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).

APD: All randomized pts in placebo and Ixekizumab. Missing values were imputed by Nonresponder imputation.
Pts who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	5.4	78.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	72.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.3
upper limit	82.5

Secondary: Percentage of Participants with a sPGA (0)

End point title	Percentage of Participants with a sPGA (0)[4]

End point description:

Static Physician Global Assessment (sPGA): The physician's global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). An sPGA assessed as either 0 or 1 represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.
An sPGA assessed as 0 represents a clinically important endpoint indicating complete resolution of plaque psoriasis.

APD:All randomized participants in placebo and Ixekizumab arms. Missing values were imputed by Nonresponder imputation.
Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	1.8	52.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	50.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.6
upper limit	60.2

Secondary: Percentage of Participants with a 100% Improvement in Psoriasis Area and Severity Index (PASI 100)

End point title	Percentage of Participants with a 100% Improvement in Psoriasis Area and Severity Index (PASI 100)[5]

End point description:

PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
Fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement): 0 = 0% (clear), 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to 90%, 6 = 90% to 100%.
Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).

APD: All randomized pts in placebo and Ixekizumab.Missing values were imputed by Nonresponder imputation.
Pts who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	1.8	49.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	47.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	38
upper limit	57.6

Secondary: Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75)

End point title	Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75)[6]

End point description:

PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe Fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement): 0 = 0% (clear), 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to 90%, 6 = 90% to 100%. Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).

APD: All randomized pts in placebo and Ixekizumab. Missing values were imputed by Nonresponder imputation.
Pts who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	14.3	75.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	45
Confidence interval	
level	95 %
sides	2-sided
lower limit	33.2
upper limit	56.8

Secondary: Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1)

End point title	Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1)[7]

End point description:

Static Physician Global Assessment (sPGA): The physician's global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5). An sPGA assessed as either 0 or 1 represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.

APD: All randomized participants in placebo and Ixekizumab arms. Missing values were imputed by Nonresponder imputation.
Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 4

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	7.1	47.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	40.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.3
upper limit	52

Secondary: Percentage of Participants with an Improvement of ≥4 in those who had a Baseline Itch Numeric Rating Scale (NRS) Score of ≥4

End point title	Percentage of Participants with an Improvement of ≥4 in those who had a Baseline Itch Numeric Rating Scale (NRS) Score of ≥4[8]

End point description:

Itch Numeric Rating Scale (NRS): is a single-item, patient-reported outcome (PRO) measure designed to capture the overall severity of a participant's itching due to his/her psoriasis by having the patient circle the integer that describes the worst level of itching in the past 24 hours on an 11-point NRS anchored at 0 representing "no itching" and 10 representing "worst itch imaginable.

APD: All randomized participants with baseline Itch NRS Score >=4 in placebo and Ixekizumab arms. Missing values were imputed by NRI. Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	83		
Units: percentage of participants				
number (not applicable)	20.0	71.1		

Statistical analyses

Statistical analysis title	Statistical Anlaysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	51.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.3
upper limit	66.9

Secondary: Percentage of Participants Achieving Children’s Dermatology Life Quality Index (CDLQI)/Dermatology Life Quality Index (DLQI) (0/1)

End point title	Percentage of Participants Achieving Children’s Dermatology Life Quality Index (CDLQI)/Dermatology Life Quality Index (DLQI) (0/1)[9]

End point description:

DLQI is a validated, dermatology-specific, patient reported measure that evaluates participant's health-related quality of life. It consists of 10 items that are grouped in 6 domains: symptoms & feelings, daily activities, leisure, work & school , personal relationships, & treatment. The recall period of this scale is over the "last week." Response categories and corresponding scores are:
Very much = 3, A lot = 2, A little = 1, Not at all = 0, Not relevant = 0. A DLQI total score is calculated by summing all 10 items responses, and has a range of 0 to 30 (higher scores are indicative of greater impairment). CDLQI questionnaire is designed for use in children (4 to 16 years of age). It consists of 10 items that are grouped into 6 domains: symptoms & feelings, leisure, school or holidays, personal relationships, sleep, & treatment. A CDLQI total score is calculated by summing all 10 items responses, and has a range of 0 to 30 (higher scores are indicative of greater impairment).

End point type	Secondary

End point timeframe:

Week 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	115		
Units: percentage of participants				
number (not applicable)	23.2	64.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	41.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	27
upper limit	55.2

Secondary: Change from Baseline on the Nail Psoriasis Severity Index (NAPSI)

End point title	Change from Baseline on the Nail Psoriasis Severity Index (NAPSI)[10]

End point description:

NAPSI is a numeric, reproducible, objective tool for evaluation of nail psoriasis. This scale was used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. Both fingernail and toenail involvement were assessed.The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each nail is given a score for nail bed psoriasis (0 to 4) and nail matrix psoriasis (0 to 4), depending on the presence (score of 1) or absence (score of 0) of any of the features of nail bed and nail matrix psoriasis in each quadrant:
0 = None
1 = present in one quadrant of nail
2 = present in two quadrants of nail
3 = present in three quadrants of nail
4 = present in four quadrants of nail
NAPSI score of a nail is the sum of scores in nail bed and nail matrix from each quadrant (maximum of 8). Each nail is evaluated, and the sum of all the fingernails and toenails is the total NAPSI score ranging from 0 (no nail Psoriasis).

End point type	Secondary

End point timeframe:

Baseline, Week 12

All randomized pts with baseline & post baseline NAPSI score.LSMean was calculated using treatment, region, baseline sPGA score,baseline weight category, baseline value, visit, treatment-by-visit, & baseline-by-visit as fixed factors.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	34		
Units: score on a scale				
least squares mean (standard error)	0.17 (± 5.331)	-16.87 (± 3.110)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-17.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.7
upper limit	-5.38
Variability estimate	Standard error of the mean
Dispersion value	5.747

Secondary: Change from Baseline on the Psoriasis Scalp Severity Index (PSSI)

End point title	Change from Baseline on the Psoriasis Scalp Severity Index (PSSI)[11]

End point description:

The scalp was assessed for erythema (redness), induration (hardness), and desquamation (shedding of skin) and percentage of area affected as follows:
Erythema, Induration and Desquamation:
0 = Absent
1 = Slight
2 = Moderate
3 = Severe
4 = Severest Possible
Percent of Scalp Involved:
1 = <10%
2 = 10% – 29%
3 = 30% – 49%
4 = 50% – 69%
5 = 70% – 89%
6 = 90% – 100%

The PSSI score is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score for the extent of scalp area involved (percent of scalp involved). The range is 0 (no psoriasis) to 72 (Most severe Disease).
LSMean was calculated using mixed model repeated measures (MMRM) model treatment, region, baseline sPGA score, baseline weight category, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors.

End point type	Secondary

End point timeframe:

Baseline, Week 12

APD: All randomized pts with baseline & post-baseline PSSI score in placebo and Ixekizumab arms.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	102		
Units: score on a scale				
least squares mean (standard error)	-12.28 (± 2.572)	-27.64 (± 2.320)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.69
upper limit	-12.04
Variability estimate	Standard error of the mean
Dispersion value	1.682

Secondary: Change from Baseline on the Palmoplantar Psoriasis Severity Index (PPASI)

End point title	Change from Baseline on the Palmoplantar Psoriasis Severity Index (PPASI)[12]

End point description:

PPASI was used if the participant has palmoplantar psoriasis at baseline. Both the palms & soles on each hand & foot was assessed for erythema, induration, desquamation & percentage of area affected as

follows:
Erythema (E), Induration (I), & Desquamation (D):
0 = None, 1 = Slight, 2 = Moderate, 3 = Severe, 4 = Very Severe
Percent of Palm and Sole Area Covered:
0 = None, 1 = <10%, 2 = 10% – 29%, 3 = 30% – 49%, 4 = 50% – 69%, 5 = 70% – 89%, 6 = 90% – 100%
PPASI score is a composite score derived from the sum scores for E, I, & D multiplied by a score for the extent of palm & sole area involvement. The range is 0 (no psoriasis) to 72 (most severe disease).
APD: All randomized participants with baseline PPASI score in placebo and Ixekizumab arms. LSMean was calculated using MMRM with treatment, region, baseline sPGA score, baseline weight category, baseline value, visit, treatment-by-visit, and baseline-by-visit interactions as fixed factors.

End point type	Secondary

End point timeframe:

Baseline, Week 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Placebo	Ixekizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	17		
Units: score on a scale				
least squares mean (standard error)	6.89 (± 3.37)	-5.11 (± 2.148)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ixekizumab
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-12.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.11
upper limit	-3.9
Variability estimate	Standard deviation
Dispersion value	3.853

Secondary: Number of Participants with Anti-Ixekizumab Antibodies

End point title	Number of Participants with Anti-Ixekizumab Antibodies

End point description:

Number of participants with anti-ixekizumab antibodies

End point type	Secondary

End point timeframe:

Baseline through Week 48

End point values	Placebo	Ixekizumab	Open-Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56[13]	115[14]	30[15]	
Units: Number of Participants				
number (not applicable)	99999	99999	99999	

Notes:

[13] - Results will be reported after LPV.
99999=NA

[14] - Results will be reported after LPV.
99999=NA

[15] - Results will be reported after LPV.
99999=NA

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Trough Ixekizumab Concentration at Steady State (Ctrough ss)

End point title	Pharmacokinetics (PK): Trough Ixekizumab Concentration at Steady State (Ctrough ss)[16]

End point description:

Pharmacokinetics (PK): Trough Ixekizumab Concentration at Steady State (Ctrough ss).

APD: All randomized participants in Ixekizumab week 12 PK samples.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, analysis was planned only for placebo & Ixekizumab arms.

End point values	Ixekizumab			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)	3.03 (± 106)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75) (Etanercept approved countries)

End point title	Percentage of Participants with a ≥75% Improvement in Psoriasis Area and Severity Index (PASI 75) (Etanercept approved countries)

End point description:

PASI combines assessments of the extent of body surface involvement in 4 regions (head & neck(h), trunk(t), arms(u), legs(l)) & severity of scaling (S), redness (R), & plaque induration/infiltration (thickness, T) in each region. Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement up to 4 for severe involvement): 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
Fraction of total BSA affected is graded on a 0-6 scale (0 for no involvement to 6 for 90% - 100% involvement): 0 = 0% (clear), 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to 90%, 6 = 90% to 100%.
Overall score ranges from 0 (no psoriasis) to 72 (most severe disease).

Missing values were imputed by Nonresponder imputation.
Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

APD: All randomized participants in Etanercept approved countries per protocol addendum.

End point values	Placebo	Ixekizumab	Open-Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	38	30	
Units: percentage of participants				
number (not applicable)	26.3	84.2	63.3	

Statistical analyses

Statistical analysis title	Statistical Anlaysis 1
Comparison groups	Open-Label Etanercept v Ixekizumab
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	41.7

Secondary: Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1) (Etanercept approved countries)

End point title	Percentage of Participants with a Static Physician Global Assessment (sPGA) (0,1) (Etanercept approved countries)

End point description:

Static Physician Global Assessment (sPGA): The physician’s global assessment of the Participant's psoriasis lesions at a given time point. Plaques are assessed for induration, erythema, and scaling, and an overall rating of psoriasis severity is given using the anchors of clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5).
An sPGA assessed as either 0 or 1 represents a clinically meaningful response of minimal plaque severity or complete resolution of plaque psoriasis.

APD: All randomized participants in Etanercept approved countries per protocol addendum. Missing values were imputed by Nonresponder imputation.
Participants who do not meet the clinical response criteria or have missing clinical response data or without at least 1 post-baseline observation are considered as nonresponders for NRI analysis.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Ixekizumab	Open-Label Etanercept	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	38	30	
Units: percentage of participants				
number (not applicable)	5.3	76.3	53.3	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Open-Label Etanercept v Ixekizumab
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	45.4

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 weeks	
Adverse event reporting additional description:	
All randomized participants.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo for Ixekizumab by subcutaneous injection.	
Reporting group title	Open-Label Etanercept
Reporting group description:	
Participants with >50kg received 160mg Ixekizumab at week 0 followed by 80mg Ixekizumab every four weeks (Q4W) from week 4 to 8 followed by 80mg ixekizumab and placebo injection at week 12 by subcutaneous injection. Participants with 25 to 50kg received 80mg Ixekizumab at week 0 followed by 40mg Ixekizumab Q4W from week 4 to 8 followed by 40mg ixekizumab and placebo injection at week 12 by subcutaneous injection. Participants with >25kg received 40mg Ixekizumab at week 0 followed by 20mg Ixekizumab Q4W from week 4 to 8 followed by 20mg ixekizumab and placebo injection at week 12 by subcutaneous injection.	
Reporting group title	Ixekizumab
Reporting group description:	
Participants received 0.8mg/kg Etanercept not exceeding 50mg per dose every week from week 0 to week 11 by subcutaneous injection.	

Serious adverse events	Placebo	Open-Label Etanercept	Ixekizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)	1 / 30 (3.33%)	1 / 115 (0.87%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
accidental overdose			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	0 / 30 (0.00%)	1 / 115 (0.87%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
overdose			
alternative dictionary used:			

MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	1 / 30 (3.33%)	0 / 115 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Open-Label Etanercept	Ixekizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 56 (14.29%)	5 / 30 (16.67%)	38 / 115 (33.04%)
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 56 (1.79%)	1 / 30 (3.33%)	12 / 115 (10.43%)
occurrences (all)	2	1	13
General disorders and administration site conditions			
injection site reaction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	0 / 30 (0.00%)	11 / 115 (9.57%)
occurrences (all)	0	0	16
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	0 / 30 (0.00%)	6 / 115 (5.22%)
occurrences (all)	0	0	6
nausea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 56 (1.79%)	0 / 30 (0.00%)	6 / 115 (5.22%)
occurrences (all)	1	0	6
Infections and infestations			
influenza			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	2 / 30 (6.67%)	2 / 115 (1.74%)
occurrences (all)	0	2	2
nasopharyngitis			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 56 (7.14%)	0 / 30 (0.00%)	13 / 115 (11.30%)
occurrences (all)	4	0	15
pharyngitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 56 (0.00%)	2 / 30 (6.67%)	2 / 115 (1.74%)
occurrences (all)	0	2	2
upper respiratory tract infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 56 (7.14%)	0 / 30 (0.00%)	6 / 115 (5.22%)
occurrences (all)	4	0	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported