Clinical trial results:
Multi-center, double-blind, randomised, placebo-controlled, phase IIb dose-finding study to evaluate efficacy and safety of different subcutaneous doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis (PPP)

Summary

EudraCT number	2018-003078-28
Trial protocol	BE DE FR CZ PL GB
Global end of trial date	28 July 2021

Results information

Result version number	v1 (current)
This version publication date	17 July 2022
First version publication date	17 July 2022

Trial information

Trial identification

Sponsor protocol code	1368-0016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04015518
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	16 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2020
Global end of trial reached?	Yes
Global end of trial date	28 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to provide dose-ranging data for 4 dose regimens of spesolimab (with each regimen consisting of a loading and a separate maintenance subcutaneous dose) compared to placebo on the primary endpoint of percentage change from baseline in PPP Area and Severity Index (PPP ASI) at Week 16. Supportive dose-ranging assessments were done on pre-specified secondary endpoints.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2019
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	Australia: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	200
EEA total number of subjects	68

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)	163
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, parallel-design trial comparing 5 treatment arms over 52 weeks. Randomisation was stratified for Japan versus non-Japan. Patients who completed the treatment period, per investigator judgement, could continue treatment with spesolimab in the open-label extension trial 1368-0024.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo & Spesolimab

Arm description:

Subcutaneous injections of placebo matching Spesolimab, with subcutaneous injections of Spesolimab starting at week 16, for a total treatment time of 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo matching Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of placebo matching Spesolimab until Week 16.

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of Spesolimab starting at week 16, for a total treatment time until week 52.

Arm title	Spesolimab ‘Speso Low’

Arm description:

Subcutaneous injections of Spesolimab in a low dose scheme for a total treatment time of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of Spesolimab in a low dose scheme for a total treatment time of 52 weeks.

Arm title	Spesolimab ‘Speso Medium-low’

Arm description:

Subcutaneous injections of Spesolimab in a medium-low dose scheme for a total treatment time of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of Spesolimab in a medium-low dose scheme for a total treatment time of 52 weeks.

Arm title	Spesolimab ‘Speso Medium-high’

Arm description:

Subcutaneous injections of Spesolimab in a medium-high dose scheme for a total treatment time of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of Spesolimab in a medium-high dose scheme for a total treatment time of 52 weeks.

Arm title	Spesolimab ‘Speso High’

Arm description:

Subcutaneous injections of Spesolimab in a high dose scheme for a total treatment time of 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of Spesolimab in a high dose scheme for a total treatment time of 52 weeks.

Number of subjects in period 1[1]	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'
Started	43	22	21
Full analysis set (FAS)	43	22	21
Completed	32	19	18
Not completed	11	3	3
Personal reasons	1	-	-
Could not keep appointments due to work	1	-	-
Prostate carcinoma	1	-	-
Patient wants to discontinue treatment	-	-	-
Patient did not come for consecutive visits	-	1	-
Withdrew consent	1	-	-
Difficult for patient to come to the hospital	-	-	-
Consent withdrawn by subject	-	1	-
not willing to travel due to Covid-19	-	-	1
Adverse event, non-fatal	6	1	1
Pregnancy	-	-	-
Lost to follow-up	-	-	-
Lack of efficacy	1	-	1

Number of subjects in period 1[1]	Spesolimab 'Speso Medium-high'	Spesolimab 'Speso High'
Started	22	44
Full analysis set (FAS)	22	44
Completed	17	32
Not completed	5	12
Personal reasons	-	1
Could not keep appointments due to work	-	-
Prostate carcinoma	-	-
Patient wants to discontinue treatment	1	-
Patient did not come for consecutive visits	-	-
Withdrew consent	-	-
Difficult for patient to come to the hospital	-	1
Consent withdrawn by subject	1	1
not willing to travel due to Covid-19	-	-
Adverse event, non-fatal	3	3
Pregnancy	-	1
Lost to follow-up	-	1

Lack of efficacy	-	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of the 200 screened subjects 152 subjects were randomized and treated.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo & Spesolimab
Reporting group description:	
Subcutaneous injections of placebo matching Spesolimab, with subcutaneous injections of Spesolimab starting at week 16, for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Low'
Reporting group description:	
Subcutaneous injections of Spesolimab in a low dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Medium-low'
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-low dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Medium-high'
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-high dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso High'
Reporting group description:	
Subcutaneous injections of Spesolimab in a high dose scheme for a total treatment time of 52 weeks.	

Reporting group values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'
Number of subjects	43	22	21
Age categorical			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
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)	32	18	21
From 65-84 years	11	4	0
85 years and over	0	0	0
Age Continuous			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: years			
arithmetic mean	57.7	54.2	51.6
standard deviation	± 10.1	± 12.3	± 7.9
Sex: Female, Male			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Participants			
Female	35	15	16
Male	8	7	5

Race (NIH/OMB)			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	18	9	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	21	11	10
More than one race	0	0	0
Unknown or Not Reported	3	2	2
Ethnicity (NIH/OMB)			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	40	20	19
Unknown or Not Reported	3	2	2
Palmoplantar Pustulosis Area and Severity Index (PPP ASI)			
The PPP ASI is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation). Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Score on a scale			
arithmetic mean	27.07	23.85	23.62
standard deviation	± 12.44	± 9.42	± 11.02

Reporting group values	Spesolimab 'Speso Medium-high'	Spesolimab 'Speso High'	Total
Number of subjects	22	44	152
Age categorical			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
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)	19	35	125
From 65-84 years	3	9	27
85 years and over	0	0	0
Age Continuous			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: years			
arithmetic mean	52.8	53.4	
standard deviation	± 9.2	± 13.0	-

Sex: Female, Male			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Participants			
Female	17	27	110
Male	5	17	42
Race (NIH/OMB)			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	15	60
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	12	26	80
More than one race	0	0	0
Unknown or Not Reported	1	3	11
Ethnicity (NIH/OMB)			
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	21	41	141
Unknown or Not Reported	1	3	11
Palmoplantar Pustulosis Area and Severity Index (PPP ASI)			
The PPP ASI is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation). Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.			
Units: Score on a scale			
arithmetic mean	26.65	24.00	
standard deviation	± 11.20	± 10.25	-

End points

End points reporting groups

Reporting group title	Placebo & Spesolimab
Reporting group description:	
Subcutaneous injections of placebo matching Spesolimab, with subcutaneous injections of Spesolimab starting at week 16, for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Low'
Reporting group description:	
Subcutaneous injections of Spesolimab in a low dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Medium-low'
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-low dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso Medium-high'
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-high dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Spesolimab 'Speso High'
Reporting group description:	
Subcutaneous injections of Spesolimab in a high dose scheme for a total treatment time of 52 weeks.	

Primary: The percentage change in Palmoplantar Pustulosis Area and Severity Index (PPP ASI) at Week 16 from baseline

End point title	The percentage change in Palmoplantar Pustulosis Area and Severity Index (PPP ASI) at Week 16 from baseline
End point description:	
PPP ASI is a tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation): Percent change from baseline is calculated as (PPP ASI current - PPP ASI baseline) / PPP ASI baseline * 100%. LS means, differences and confidence intervals were estimated by (Restricted maximum likelihood) based MMRM with fixed, categorical effects of treatment at each visit, region and continuous effect of baseline at each visit as well as random effects of subject. Values post rescue medication or 6 weeks following last study treatment before discontinuation were censored. Unstructured covariance matrix was used. Full Analysis Set (FAS): all patients who were randomised and received at least one dose of study drug. Only subjects with non-missing endpoint data were included.	
End point type	Primary
End point timeframe:	
week 0 (baseline) and week 16	

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	20	21	20
Units: Percentage of change in PPP ASI				
least squares mean (confidence interval 95%)	-33.6 (-43.5 to -23.7)	-44.2 (-57.8 to -30.6)	-48.3 (-61.8 to -34.7)	-46.2 (-59.9 to -32.6)

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of change in PPP ASI				
least squares mean (confidence interval 95%)	-38.9 (-48.5 to -29.3)			

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2179
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-10.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.4
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	8.5

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0883
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	2.2
Variability estimate	Standard error of the mean
Dispersion value	8.5

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1414
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-12.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.4
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	8.5

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4514
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-5.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	8.6
Variability estimate	Standard error of the mean
Dispersion value	7

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.212 [1]
Method	MCP-Mod linear model fit

Notes:

[1] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1057 [2]
Method	MCP-Mod Emax model fit

Notes:

[2] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5241 [3]
Method	MCP-Mod Exponential model fit

Notes:

[3] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2773 [4]
Method	MCP-Mod Logistic model fit

Notes:

[4] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3867 [5]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[5] - Adjusted for multiplicity.

Secondary: Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 4

End point title	Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 4

End point description:

Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 4. The PPP Pain VAS is a unidimensional measure of pain intensity due to palmoplantar pustulosis on palms and/or soles. It is a continuous scale comprised of a horizontal or vertical line, 10 centimeters (cm) in length, anchored by word descriptors at each end (score ranges from "no pain" at 0 cm to "very severe pain" at 10 cm). The patient was asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain.
Least square (LS) means, differences and confidence intervals were estimated by (Restricted maximum likelihood)−based MMRM including the fixed, categorical effects of treatment at each visit, region and

the continuous effect of baseline at each visit as well as random effects of subject. Values post rescue medication or 6 weeks following last study treatment before discontinuation were censored. Unstructured covariance matrix was used.
FAS

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 4.

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	20	21	20
Units: Score on a scale				
least squares mean (confidence interval 95%)	-9.3 (-17.0 to -1.6)	-15.4 (-26.1 to -4.8)	-14.7 (-25.7 to -3.8)	-12.8 (-23.5 to -2.1)

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Score on a scale				
least squares mean (confidence interval 95%)	-18.7 (-26.3 to -11.1)			

Statistical analyses

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3
upper limit	7.1
Variability estimate	Standard error of the mean
Dispersion value	6.7

Statistical analysis title	Statistical analysis 11
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	8
Variability estimate	Standard error of the mean
Dispersion value	6.8

Statistical analysis title	Statistical analysis 12
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	9.7
Variability estimate	Standard error of the mean
Dispersion value	6.6

Statistical analysis title	Statistical analysis 13
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-9.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.3
upper limit	1.4
Variability estimate	Standard error of the mean
Dispersion value	5.5

Secondary: Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 16

End point title	Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 16

End point description:

Change from baseline in Palmoplantar Pustulosis Pain Visual Analogue Scale (VAS) score at Week 16.
The PPP Pain VAS is a unidimensional measure of pain intensity due to palmoplantar pustulosis on palms and/or soles. It is a continuous scale comprised of a horizontal or vertical line, 10 centimeters (cm) in length, anchored by word descriptors at each end (score ranges from "no pain" at 0 cm to "very severe pain" at 10 cm). The patient was asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain.
Least square (LS) means, differences and confidence intervals were estimated by (Restricted maximum likelihood)−based MMRM including the fixed, categorical effects of treatment at each visit, region and the continuous effect of baseline at each visit as well as random effects of subject. Values post rescue medication or 6 weeks following last study treatment before discontinuation were censored.
Unstructured covariance matrix was used.
FAS

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16.

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	20	21	20
Units: Score on a scale				
least squares mean (confidence interval 95%)	-14.7 (-22.7 to -6.7)	-18.7 (-29.8 to -7.7)	-13.8 (-24.8 to -2.8)	-18.9 (-30.0 to -7.8)

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Score on a scale				
least squares mean (confidence interval 95%)	-22.4 (-30.2 to -14.6)			

Statistical analyses

Statistical analysis title	Statistical analysis 14
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5595
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	9.6
Variability estimate	Standard error of the mean
Dispersion value	6.9

Statistical analysis title	Statistical analysis 15
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8968
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	14.5
Variability estimate	Standard error of the mean
Dispersion value	6.9

Statistical analysis title	Statistical analysis 16
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5456
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.9
upper limit	9.5
Variability estimate	Standard error of the mean
Dispersion value	6.9

Statistical analysis title	Statistical analysis 17
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab ‘Speso High’
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1762
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	3.5
Variability estimate	Standard error of the mean
Dispersion value	5.7

Statistical analysis title	Statistical analysis 18
Statistical analysis description:	
A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).	
Comparison groups	Placebo & Spesolimab v Spesolimab ‘Speso Low’ v Spesolimab ‘Speso Medium-low’ v Spesolimab ‘Speso Medium-high’ v Spesolimab ‘Speso High’

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1726 [6]
Method	MCP-Mod linear model fit

Notes:

[6] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2353 [7]
Method	MCP-Mod Emax model fit

Notes:

[7] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1346 [8]
Method	MCP-Mod Exponential model fit

Notes:

[8] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.195 [9]
Method	MCP-Mod Logistic model fit

Notes:

[9] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1681 [10]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[10] - Adjusted for multiplicity.

Secondary: Palmoplantar Pustulosis Severity Index (PPP SI) change from baseline at Week 16

End point title	Palmoplantar Pustulosis Severity Index (PPP SI) change from baseline at Week 16

End point description:

PPP SI change from baseline at Week 16. The PPP SI is based on the severity score of individual components (erythema, pustules, and scaling/desquamation) of PPP ASI assessments. The most severely affected area based on pustules was identified by the investigator at baseline and assessed at all subsequent visits. The PPP SI was calculated by summing up the individual components of PPP ASI assessment (range 0 (best) to 12 (worst)) at each visit for the identified location.

Least square (LS) means, differences and confidence intervals were estimated by (Restricted maximum likelihood)−based Mixed effect model for repeated measurements (MMRM) including the fixed, categorical effects of treatment at each visit, region and the continuous effect of baseline at each visit as well as random effects of subject. Values post rescue medication or 6 weeks following last study treatment before discontinuation were censored. Unstructured covariance matrix was used.

Full Analysis Set was used.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16.

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	20	21	20
Units: Score on a scale				
least squares mean (confidence interval 95%)	-2.7 (-3.4 to -2.0)	-3.3 (-4.3 to -2.4)	-3.2 (-4.2 to -2.3)	-3.5 (-4.4 to -2.5)

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Score on a scale				
least squares mean (confidence interval 95%)	-2.8 (-3.4 to -2.1)			

Statistical analyses

Statistical analysis title	Statistical analysis 23
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2812
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Statistical analysis 24
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3357
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Statistical analysis 25
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1809
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Statistical analysis 26
Statistical analysis description:	
Kenward-Roger was used to estimate denominator degrees of freedom. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8322
Method	Mixed models analysis
Parameter estimate	Difference of adjusted means
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.9
Variability estimate	Standard error of the mean
Dispersion value	0.5

Statistical analysis title	Statistical analysis 27

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4035 [11]
Method	MCP-Mod linear model fit

Notes:

[11] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 28

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2563 [12]
Method	MCP-Mod Emax model fit

Notes:

[12] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 29

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.681 [13]
Method	MCP-Mod Exponential model fit

Notes:

[13] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 30

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4665 [14]
Method	MCP-Mod Logistic model fit

Notes:

[14] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 31

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5565 [15]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[15] - Adjusted for multiplicity.

Secondary: Number of patients achieving a 50% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI50)

End point title	Number of patients achieving a 50% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI50)

End point description:

Number of patients achieving a 50% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI50). The PPP ASI is an investigator assessment of the extent and severity of palmoplantar pustulosis lesions on the palms and soles in PPP patients. This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation). When (PPP ASI baseline - PPP ASI current)/ PPP ASI baseline * 100% >= 50%, PPP ASI50 = 1.

Full Analysis Set (FAS): This patient set includes all patients who were randomised and received at least one dose of study drug. Only subjects with non missing endpoint data were included.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	22	21	22
Units: Participants	12	7	10	12

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Participants	18			

Statistical analyses

Statistical analysis title	Statistical analysis 32

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.281

Statistical analysis title	Statistical analysis 33

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.432

Statistical analysis title	Statistical analysis 34

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.496

Statistical analysis title	Statistical analysis 35

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.314

Statistical analysis title	Statistical analysis 36

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0613 [16]
Method	MCP-Mod linear model fit

Notes:

[16] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 38

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 25% of the maximum effect was achieved at the "medium-low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1449 [17]
Method	MCP-Mod Exponential model fit

Notes:

[17] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 37

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 70% of the maximum effect was achieved at the "low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0628 [18]
Method	MCP-Mod Emax model fit

Notes:

[18] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 39

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested

using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 20% of maximum effect was achieved at the "low dose", 95% of maximum effect was achieved at "medium high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.046 [19]
Method	MCP-Mod Logistic model fit

Notes:

[19] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 40

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 10% of the maximum effect was achieved at "low dose", 80% of the maximum effect was achieved at the "medium-high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0677 [20]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[20] - Adjusted for multiplicity.

Secondary: Number of patients achieving a 75% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI75)

End point title	Number of patients achieving a 75% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI75)

End point description:

Number of patients achieving a 75% decrease from baseline in Palmoplantar Pustulosis Area and Severity Index score at week 16 (PPP ASI75). The PPP ASI is an investigator assessment of the extent and severity of palmoplantar pustulosis lesions on the palms and soles in PPP patients. This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation). When (PPP ASI baseline - PPP ASI current)/ PPP ASI baseline * 100% >= 75%, PPP ASI75 = 1.

Full Analysis Set (FAS): This patient set includes all patients who were randomised and received at least one dose of study drug. Only subjects with non missing endpoint data were included.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	22	21	22
Units: Participants	3	3	6	4

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Participants	9			

Statistical analyses

Statistical analysis title	Statistical analysis 41
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.256

Statistical analysis title	Statistical analysis 42
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.188
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.405

Statistical analysis title	Statistical analysis 43
Statistical analysis description: Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.303

Statistical analysis title	Statistical analysis 44
Statistical analysis description: Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.25

Statistical analysis title	Statistical analysis 45
Statistical analysis description: A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0536 [21]
Method	MCP-Mod linear model fit

Notes:

[21] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 46

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 70% of the maximum effect was achieved at the "low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0476 [22]
Method	MCP-Mod Emax model fit

Notes:

[22] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 47

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 25% of the maximum effect was achieved at the "medium-low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1076 [23]
Method	MCP-Mod Exponential model fit

Notes:

[23] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 48

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 20% of maximum effect was achieved at the "low dose", 95% of maximum effect was achieved at "medium high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0606 [24]
Method	MCP-Mod Logistic model fit

Notes:

[24] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 49

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 10% of the maximum effect was achieved at "low dose", 80% of the maximum effect was achieved at the "medium-high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0824 [25]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[25] - Adjusted for multiplicity.

Secondary: Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) clear/almost clear (0 or 1) at Week 16

End point title	Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) clear/almost clear (0 or 1) at Week 16

End point description:

Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) clear/almost clear (0 or 1) at Week 16. The PPP PGA relies on investigator assessment of the patient's skin presentation on the palms and soles. The investigator scored the individual components (erythema, pustules, and scaling/crusting) from 0 (best) to 4 (worst) as clear, almost clear, mild, moderate or severe. PPP PGA categorization is based on the mean of the four individual components.

Full Analysis Set (FAS): This patient set includes all patients who were randomised and received at least one dose of study drug. Only subjects with non missing endpoint data were included.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	22	21	22
Units: Participants	2	6	4	4

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Participants	9			

Statistical analyses

Statistical analysis title	Statistical analysis 50
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.422

Statistical analysis title	Statistical analysis 52
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.328

Statistical analysis title	Statistical analysis 53

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.282

Statistical analysis title	Statistical analysis 51

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.339

Statistical analysis title	Statistical analysis 54

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0333 [26]
Method	MCP-Mod linear model fit

Notes:

[26] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 55

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 70% of the maximum effect was achieved at the "low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0221 [27]
Method	MCP-Mod Emax model fit

Notes:

[27] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 56

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 25% of the maximum effect was achieved at the "medium-low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0707 [28]
Method	MCP-Mod Exponential model fit

Notes:

[28] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 57

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 20% of maximum effect was achieved at the "low dose", 95% of maximum effect was achieved at "medium high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0578 [29]
Method	MCP-Mod Logistic model fit

Notes:

[29] - Adjusted for multiplicity.

	Statistical analysis 58

Statistical analysis title	

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 10% of the maximum effect was achieved at "low dose", 80% of the maximum effect was achieved at the "medium-high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0771 [30]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[30] - Adjusted for multiplicity.

Secondary: Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) pustules clear/almost clear (0 or 1) at Week 16

End point title	Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) pustules clear/almost clear (0 or 1) at Week 16

End point description:

Number of patients with Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) pustules clear/almost clear (0 or 1) at Week 16. The PPP PGA relies on investigator assessment of the patient's skin presentation on the palms and soles. The investigator scored the pustules from 0 (best) to 4 (worst) as clear, almost clear, mild, moderate or severe.

Full Analysis Set (FAS): This patient set includes all patients who were randomised and received at least one dose of study drug. Only subjects with non missing endpoint data were included.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 16

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	22	21	22
Units: Participants	5	7	6	8

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: Participants	14			

Statistical analyses

Statistical analysis title	Statistical analysis 59
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.427

Statistical analysis title	Statistical analysis 60
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.401

Statistical analysis title	Statistical analysis 61
Statistical analysis description:	
Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.248

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.471

Statistical analysis title	Statistical analysis 62

Statistical analysis description:

Confidence intervals were calculated using the cumulative distribution function method of Reeve. Difference was calculated as Speso - placebo.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.367

Statistical analysis title	Statistical analysis 63

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0158 [31]
Method	MCP-Mod linear model fit

Notes:

[31] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 64

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 70% of the maximum effect was achieved at the "low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.012 [32]
Method	MCP-Mod Emax model fit

Notes:

[32] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 65

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 25% of the maximum effect was achieved at the "medium-low dose" regimen.

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0429 [33]
Method	MCP-Mod Exponential model fit

Notes:

[33] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 66

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 20% of maximum effect was achieved at the "low dose", 95% of maximum effect was achieved at "medium high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0229 [34]
Method	MCP-Mod Logistic model fit

Notes:

[34] - Adjusted for multiplicity.

Statistical analysis title	Statistical analysis 67

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of Spesolimab and placebo was tested using the MCP-Mod approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, Emax, exponential, logistic, Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.05). Assumed 10% of the maximum effect was achieved at "low dose", 80% of the maximum effect was achieved at the "medium-high dose".

Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low' v Spesolimab 'Speso Medium-low' v Spesolimab 'Speso Medium-high' v Spesolimab 'Speso High'

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.03 [35]
Method	MCP-Mod Sigmoid Emax model fit

Notes:

[35] - Adjusted for multiplicity.

Secondary: The percentage change in Palmoplantar Pustulosis Area and Severity Index (PPP ASI) at Week 52 from baseline

End point title	The percentage change in Palmoplantar Pustulosis Area and Severity Index (PPP ASI) at Week 52 from baseline

End point description:

The percentage change in PPP ASI at Week 52 from baseline. The PPP ASI is an investigator assessment of the extent and severity of palmoplantar pustulosis lesions on the palms and soles in PPP patients. This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 (best) to 72 (worst). It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).

LS means, differences and confidence intervals were estimated by (Restricted maximum likelihood)−based MMRM including the fixed, categorical effects of treatment at each visit, region and the continuous effect of baseline at each visit as well as random effects of subject. Values post rescue medication or 6 weeks following last study treatment before discontinuation were censored. Unstructured covariance matrix was used.

Full Analysis Set.

End point type	Secondary

End point timeframe:

week 0 (baseline) and week 52

End point values	Placebo & Spesolimab	Spesolimab 'Speso Low'	Spesolimab 'Speso Medium-low'	Spesolimab 'Speso Medium-high'
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	19	18	17
Units: Percentage of change in PPP ASI				
least squares mean (confidence interval 95%)	-54.6 (-65.8 to -43.3)	-73.3 (-87.9 to -58.6)	-73.8 (-89.1 to -58.6)	-81.2 (-96.4 to -66.1)

End point values	Spesolimab 'Speso High'			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Percentage of change in PPP ASI				
least squares mean (confidence interval 95%)	-60.0 (-70.9 to -49.2)			

Statistical analyses

Statistical analysis title	Statistical analysis 68
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Low'
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.2
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	9.3

Statistical analysis title	Statistical analysis 69
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-low'
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.3
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	9.6

Statistical analysis title	Statistical analysis 70
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso Medium-high'
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-26.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.5
upper limit	-7.8
Variability estimate	Standard error of the mean
Dispersion value	9.5

Statistical analysis title	Statistical analysis 71
Statistical analysis description: Difference was calculated as Speso - placebo.	
Comparison groups	Placebo & Spesolimab v Spesolimab 'Speso High'
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of adjusted means
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.1
upper limit	10.2
Variability estimate	Standard error of the mean
Dispersion value	7.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first until the last day of study drug administration + 112 days, up to 68 weeks.	
Adverse event reporting additional description:	
Safety analysis set (SAF): This patient set includes all patients who were randomised and received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subcutaneous injections of placebo matching Spesolimab from week 0 to 16.	
Reporting group title	Speso High
Reporting group description:	
Subcutaneous injections of Spesolimab in a high dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Speso Medium-low
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-low dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Speso Medium-high
Reporting group description:	
Subcutaneous injections of Spesolimab in a medium-high dose scheme for a total treatment time of 52 weeks.	
Reporting group title	Speso Post Placebo
Reporting group description:	
Subcutaneous injections of Spesolimab starting at week 16, for a total treatment time until week 52.	
Reporting group title	Speso Low
Reporting group description:	
Subcutaneous injections of Spesolimab in a low dose scheme for a total treatment time of 52 weeks.	

Serious adverse events	Placebo	Speso High	Speso Medium-low
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 43 (4.65%)	3 / 44 (6.82%)	5 / 21 (23.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (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

Breast cancer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pneumothorax traumatic			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			

subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dyshidrotic eczema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (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
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmoplantar pustulosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (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
Pustular psoriasis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Foot deformity			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Speso Medium-high	Speso Post Placebo	Speso Low
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)	3 / 38 (7.89%)	3 / 22 (13.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pneumothorax traumatic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dyshidrotic eczema			

subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmoplantar pustulosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pustular psoriasis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rhabdomyolysis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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	Speso High	Speso Medium-low
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 43 (55.81%)	31 / 44 (70.45%)	17 / 21 (80.95%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	0 / 21 (0.00%)
occurrences (all)	0	5	0
Contusion			
subjects affected / exposed	0 / 43 (0.00%)	4 / 44 (9.09%)	0 / 21 (0.00%)
occurrences (all)	0	4	0
Skin abrasion			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 43 (2.33%)	5 / 44 (11.36%)	0 / 21 (0.00%)
occurrences (all)	1	13	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	1 / 21 (4.76%)
occurrences (all)	0	6	2
Injection site pain			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	3 / 21 (14.29%)
occurrences (all)	10	1	18
Injection site reaction			

subjects affected / exposed	0 / 43 (0.00%)	20 / 44 (45.45%)	5 / 21 (23.81%)
occurrences (all)	0	105	20
Pyrexia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	4
Dermatitis contact			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	2 / 43 (4.65%)	0 / 44 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	2
Palmoplantar pustulosis			
subjects affected / exposed	4 / 43 (9.30%)	5 / 44 (11.36%)	1 / 21 (4.76%)
occurrences (all)	5	5	1
Pruritus			
subjects affected / exposed	1 / 43 (2.33%)	2 / 44 (4.55%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Rash			

subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 43 (0.00%)	3 / 44 (6.82%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 43 (13.95%)	3 / 44 (6.82%)	0 / 21 (0.00%)
occurrences (all)	6	3	0
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 44 (4.55%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 43 (2.33%)	1 / 44 (2.27%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Osteoarthritis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 44 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pustulotic arthro-osteitis			
subjects affected / exposed	1 / 43 (2.33%)	2 / 44 (4.55%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 43 (11.63%)	4 / 44 (9.09%)	2 / 21 (9.52%)
occurrences (all)	6	5	2
Rhinitis			

subjects affected / exposed	3 / 43 (6.98%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences (all)	5	1	0
Sinusitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 44 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 44 (2.27%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Speso Medium-high	Speso Post Placebo	Speso Low
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 22 (77.27%)	22 / 38 (57.89%)	17 / 22 (77.27%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	3 / 38 (7.89%)	2 / 22 (9.09%)
occurrences (all)	5	3	2
General disorders and administration site conditions			
Injection site erythema			

subjects affected / exposed	4 / 22 (18.18%)	2 / 38 (5.26%)	3 / 22 (13.64%)
occurrences (all)	10	4	5
Injection site pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 22 (0.00%)
occurrences (all)	1	12	0
Injection site reaction			
subjects affected / exposed	5 / 22 (22.73%)	4 / 38 (10.53%)	3 / 22 (13.64%)
occurrences (all)	15	11	23
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Dental caries			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 38 (2.63%)	3 / 22 (13.64%)
occurrences (all)	4	1	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Dermatitis contact			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Eczema			
subjects affected / exposed	1 / 22 (4.55%)	2 / 38 (5.26%)	6 / 22 (27.27%)
occurrences (all)	1	2	12
Palmoplantar pustulosis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 22 (4.55%)	1 / 38 (2.63%)	2 / 22 (9.09%)
occurrences (all)	1	1	2
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	3
Urticaria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 22 (9.09%)	4 / 38 (10.53%)	3 / 22 (13.64%)
occurrences (all)	2	5	3
Back pain			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	4 / 22 (18.18%)
occurrences (all)	3	0	4
Musculoskeletal chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 38 (2.63%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 38 (5.26%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Pustulotic arthro-osteitis			

subjects affected / exposed	2 / 22 (9.09%)	2 / 38 (5.26%)	0 / 22 (0.00%)
occurrences (all)	2	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 22 (9.09%)	3 / 38 (7.89%)	3 / 22 (13.64%)
occurrences (all)	2	4	4
Rhinitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 38 (0.00%)	0 / 22 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	1 / 22 (4.55%)
occurrences (all)	3	0	2
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 38 (0.00%)	3 / 22 (13.64%)
occurrences (all)	1	0	3

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