Clinical trial results:
Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP

Summary

EudraCT number	2018-003081-14
Trial protocol	DE BE ES NL GR FR CZ PL BG IT HR
Global end of trial date	23 November 2022
Results information	
Result version number	v1 (current)
This version publication date	07 June 2023
First version publication date	07 June 2023

Trial information

Trial identification	
Sponsor protocol code	1368-0027
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04399837
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-002475-PIP02-19
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 November 2022
Global end of trial reached?	Yes
Global end of trial date	23 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to demonstrate a non-flat dose response curve and evaluate the dose-response relationship for 3 subcutaneous (s.c.) dosing regimens of spesolimab (with each regimen consisting of a single loading dose and a separate maintenance s.c. dosing regimen) versus placebo, on the primary endpoint, the time to the first GPP flare onset up to Week 48.
The secondary objective was to demonstrate superiority versus placebo for each of spesolimab high dose (300 milligram (mg) every 4 weeks (q4w)) and spesolimab medium dose (300 mg q12w) on the primary endpoint, the time to the first generalized pustular psoriasis (GPP) flare onset up to Week 48, as well as the key secondary endpoint, the occurrence of at least one GPP flare up to Week 48.
Another objective was to evaluate safety and tolerability of multiple s.c. doses of spesolimab in patients with history of GPP.

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	08 June 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Chile: 4
Country: Number of subjects enrolled	China: 24
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Malaysia: 25
Country: Number of subjects enrolled	Mexico: 2

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Philippines: 9
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Tunisia: 8
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Viet Nam: 9
Worldwide total number of subjects	157
EEA total number of subjects	21

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)	10
Adults (18-64 years)	136
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase IIb trial comprising of 3 active doses compared to placebo in adolescents from 12 years to less than 18 years of age and adult patients with history of Generalized Pustular Psoriasis (GPP) and presenting (at screening and at randomization) with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1.

Pre-assignment

Screening details:

Subjects attended a specialist site which ensured that they (the subjects) met all inclusion and none of the exclusion criteria.
The randomization was stratified accounting for use of systemic GPP medications at randomization (yes vs. no), and the blocking factors, region (Japan vs. non-Japan) and population (adults vs. adolescents).

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	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Blinding implementation details:

To maintain the treatment blind during the trial, all patients received the blinded treatments every 4 weeks.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients were subcutaneously (SC) injected on Day 1 of Week 1 a loading dose of solution for injection of placebo matching solution for injection of spesolimab followed by a maintenance tretament which consisted of a subcutaneous injection of solution for injection of placebo matching solution for injection of spesolimab every 4 weeks (i.e. on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 of flare (R1/D1) or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Arm type	Placebo
Investigational medicinal product name	Placebo to match Solution for Injection (BI 655130)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients were subcutaneously (SC) injected on Day 1 of Week 1 a loading dose of solution for injection of placebo matching solution for injection of spesolimab followed by a maintenance tretament which consisted of a subcutaneous injection of solution for injection of placebo matching solution for injection of spesolimab every 4 weeks (i.e. on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44).

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The patients who experienced a flare were administered OL maintenance treatment if time allowed

which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 of flare (R1/D1) or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare.

Arm title	Spesolimab SC low dose

Arm description:

Patients received on Day 1 of Week 1 a loading dose which consisted of two subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300mg) and two subcutaneous injections of placebo matching solution for injection of spesolimab. The loading dose was followed by a maintenance treatment which consisted of one SC injection of 150 mg of solution for injection of spesolimab and one SC injection of placebo matching solution for injection of spesolimab every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at R1/D1 of flare or at R1/D1 and at R3/D8 of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received on Day 1 of Week 1 a loading dose which consisted of two subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300mg) and two subcutaneous injections of placebo matching solution for injection of spesolimab. The loading dose was followed by a maintenance treatment which consisted of one SC injection of 150 mg of solution for injection of spesolimab and one SC injection of placebo matching solution for injection of spesolimab every 12 weeks (i.e. at Week 12, 24 and 36).
The patients who experienced a flare during the 48 week randomised treatment period and received IV spesolimab were administered OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at R1/D1 of flare or at R1/D1 and at R3/D8.

Arm title	Spesolimab SC medium dose

Arm description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered subcutaneously every 12 weeks or every 4 weeks (intensified maintenance therapy).

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare.

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 12 weeks (i.e. at Week 12, 24 and 36).

The patients who experienced a flare during the 48 week randomised treatment period and received IV spesolimab were administered OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Arm title	Spesolimab SC high dose

Arm description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 4 weeks (i.e. at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Arm type	Experimental
Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 4 weeks (i.e. at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44).
The patients who experienced a flare during the 48 week randomised treatment period and received IV spesolimab were administered OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Investigational medicinal product name	Spesolimab
Investigational medicinal product code	BI 655130
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients who experienced a flare during the 48 week randomised treatment period were

administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare.

Number of subjects in period 1[1]	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose
Started	31	31	31
Completed	30	27	28
Not completed	1	4	3
Consent withdrawn by subject	1	2	1
Other than listed	-	2	2

Number of subjects in period 1[1]	Spesolimab SC high dose
Started	30
Completed	26
Not completed	4
Consent withdrawn by subject	1
Other than listed	3

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 157 enrolled patients only 123 were randomized.

Baseline characteristics

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients were subcutaneously (SC) injected on Day 1 of Week 1 a loading dose of solution for injection of placebo matching solution for injection of spesolimab followed by a maintenance tretament which consisted of a subcutaneous injection of solution for injection of placebo matching solution for injection of spesolimab every 4 weeks (i.e. on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 of flare (R1/D1) or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC low dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of two subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300mg) and two subcutaneous injections of placebo matching solution for injection of spesolimab. The loading dose was followed by a maintenance treatment which consisted of one SC injection of 150 mg of solution for injection of spesolimab and one SC injection of placebo matching solution for injection of spesolimab every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at R1/D1 of flare or at R1/D1 and at R3/D8 of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC medium dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered subcutaneously every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC high dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 4 weeks (i.e. at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose
Number of subjects	31	31	31
Age categorical			
Randomized Set: This patient set includes all randomized patients.			
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)	2	2	2
Adults (18-64 years)	28	27	27
From 65-84 years	1	2	2
85 years and over	0	0	0
Age Continuous			
Randomized Set: This patient set includes all randomized patients.			
Units: years			
arithmetic mean	39.5	38.9	42.9
standard deviation	± 14.0	± 16.5	± 16.7
Sex: Female, Male			
Randomized Set: This patient set includes all randomized patients.			
Units: Participants			
Female	18	20	20
Male	13	11	11
Race (NIH/OMB)			
Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	17	20	21
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	14	11	10
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
Hispanic or Latino	3	3	0
Not Hispanic or Latino	28	28	31
Unknown or Not Reported	0	0	0
Number of patients in the categories 0 or 1 of GPPGA score			
Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) relied on the clinical assessment of GPP patient’s skin presentation. The total score is calculated by taking the mean of the three subscores: 1) erythema; 2) pustules and 3) scaling/crusting which were assessed using a scale score 0 to 4 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). The final GPPGA score: 0 , if scores for all three subscores are 0, 1, if 0 < mean < 1.5; 2, if 1.5 ≤ mean < 2.5; 3, if 2.5 ≤ mean < 3.5; 4, if mean ≥ 3.5. Number of patients in the categories 0 or 1 of GPPGA score is reported.			
Units: Subjects			
GPPGA score = 0	4	2	8
GPPGA score = 1	27	29	23
Number of patients in the categories 0 or 1 of GPPGA pustules subscore			
The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustules subscore relied on clinical assessment of the Generalized Pustular Psoriasis (GPP) pustules presentation. The investigator (or qualified site personnel) scored the pustules of all GPP lesions from 0 to 4 where: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. Number of patients in the categories 0 or 1 of GPPGA pustules subscore is reported. Randomized Set.			
Units: Subjects			

GPPGA pustules subscore=0	21	23	24
GPPGA pustules subscore=1	10	8	7
Concomitant use of systemic GPP medication at randomization			
Number of patients in each category of concomitant use of systemic GPP medication at randomization (-28 days to randomization). The reported categories of concomitant use of systemic GPP medication at randomization are: Yes; No. Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
Systemic GPP medication at randomization=No	9	6	8
Systemic GPP medication at randomization=Yes	22	25	23
Psoriasis Symptom Scale (PSS) total score at baseline			
The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of 4 psoriasis symptoms in patients with moderate to severe psoriasis. The symptoms included are: pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 (no symptoms) to 16 (severe symptoms). Randomized Set.			
Units: score on a scale			
arithmetic mean	3.6	4.1	3.9
standard deviation	± 2.9	± 3.8	± 2.9
DLQI total score at baseline			
The Dermatology Quality of Life Index (DLQI) is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Response categories range from 0 (not relevant) to 3 (very much). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. Total score is obtained by summing the scores of each question resulting in a range of 0 (no effect on patient's life) to 30 (extremely large effect on patient's life). Randomized Set.			
Units: score on a scale			
arithmetic mean	7.2	7.6	6.6
standard deviation	± 5.6	± 6.7	± 5.6

Reporting group values	Spesolimab SC high dose	Total	
Number of subjects	30	123	
Age categorical			
Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	2	8	
Adults (18-64 years)	25	107	
From 65-84 years	3	8	
85 years and over	0	0	
Age Continuous			
Randomized Set: This patient set includes all randomized patients.			
Units: years			
arithmetic mean	40.2		
standard deviation	± 16.4	-	

Sex: Female, Male			
Randomized Set: This patient set includes all randomized patients.			
Units: Participants			
Female	18	76	
Male	12	47	
Race (NIH/OMB)			
Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	21	79	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	9	44	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
Hispanic or Latino	1	7	
Not Hispanic or Latino	29	116	
Unknown or Not Reported	0	0	
Number of patients in the categories 0 or 1 of GPPGA score			
Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) relied on the clinical assessment of GPP patient's skin presentation. The total score is calculated by taking the mean of the three subscores: 1) erythema; 2) pustules and 3) scaling/crusting which were assessed using a scale score 0 to 4 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). The final GPPGA score: 0 , if scores for all three subscores are 0, 1, if 0 < mean < 1.5; 2, if 1.5 ≤ mean < 2.5; 3, if 2.5 ≤ mean < 3.5; 4, if mean ≥ 3.5. Number of patients in the categories 0 or 1 of GPPGA score is reported.			
Units: Subjects			
GPPGA score = 0	3	17	
GPPGA score = 1	27	106	
Number of patients in the categories 0 or 1 of GPPGA pustules subscore			
The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustules subscore relied on clinical assessment of the Generalized Pustular Psoriasis (GPP) pustules presentation. The investigator (or qualified site personnel) scored the pustules of all GPP lesions from 0 to 4 where: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. Number of patients in the categories 0 or 1 of GPPGA pustules subscore is reported. Randomized Set.			
Units: Subjects			
GPPGA pustules subscore=0	20	88	
GPPGA pustules subscore=1	10	35	
Concomitant use of systemic GPP medication at randomization			
Number of patients in each category of concomitant use of systemic GPP medication at randomization (-28 days to randomization). The reported categories of concomitant use of systemic GPP medication at randomization are: Yes; No. Randomized Set: This patient set includes all randomized patients.			
Units: Subjects			
Systemic GPP medication at randomization=No	8	31	
Systemic GPP medication at randomization=Yes	22	92	

Psoriasis Symptom Scale (PSS) total score at baseline			
The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of 4 psoriasis symptoms in patients with moderate to severe psoriasis. The symptoms included are: pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 (no symptoms) to 16 (severe symptoms). Randomized Set.			
Units: score on a scale arithmetic mean standard deviation	 5.3 ± 3.8	 -	
DLQI total score at baseline			
The Dermatology Quality of Life Index (DLQI) is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Response categories range from 0 (not relevant) to 3 (very much). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. Total score is obtained by summing the scores of each question resulting in a range of 0 (no effect on patient's life) to 30 (extremely large effect on patient's life). Randomized Set.			
Units: score on a scale arithmetic mean standard deviation	 11.1 ± 6.9	 -	

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Patients were subcutaneously (SC) injected on Day 1 of Week 1 a loading dose of solution for injection of placebo matching solution for injection of spesolimab followed by a maintenance tretament which consisted of a subcutaneous injection of solution for injection of placebo matching solution for injection of spesolimab every 4 weeks (i.e. on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 of flare (R1/D1) or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC low dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of two subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300mg) and two subcutaneous injections of placebo matching solution for injection of spesolimab. The loading dose was followed by a maintenance treatment which consisted of one SC injection of 150 mg of solution for injection of spesolimab and one SC injection of placebo matching solution for injection of spesolimab every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at R1/D1 of flare or at R1/D1 and at R3/D8 of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC medium dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered subcutaneously every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Spesolimab SC high dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 4 weeks (i.e. at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Subject analysis set title	Spesolimab IV SD
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who took a single dose (SD) of rescue treatment of 900 milligram (mg) of spesolimab administered intravenously (IV) at Day 1 of flare (R1/D1) because of a GPP flare during the 48-week treatment randomised period.

Subject analysis set title	Spesolimab IV DD
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who took two doses (DD)

of rescue treatment of spesolimab each 900 milligram (mg) of spesolimab administered intravenously (IV) at Day 1 and at Day 8 of flare (R1/D1 and R3/D8) because of a GPP flare during the 48-week treatment randomised period.

Subject analysis set title	Spesolimab OL SC
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who experienced a flare during the 48-week randomised treatment period and were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at either Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare and then followed by maintenance treatment which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Subject analysis set title	Spesolimab SC low dose (safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all the patients randomized to the arm “Spesolimab SC low dose” plus one patient who was randomized to “Placebo” arm but received active spesolimab dose.

Subject analysis set title	Placebo (safety)
Subject analysis set type	Safety analysis

Subject analysis set description:

This arm includes all the patients who were randomized to the arm “Placebo" and were administered placebo matching solution for injection of Spesolimab.

Primary: Time to first Generalized Pustular Psoriasis (GPP) flare

End point title	Time to first Generalized Pustular Psoriasis (GPP) flare

End point description:

A GPP flare was defined as increase in GPP Physician Global Assessment (GPPGA) score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48. Use of rescue medication, or investigator-prescribed SoC for GPP worsening, was considered to represent a GPP flare onset.
GPPGA relied on clinical assessment of the GPP patient’s skin presentation. The GPPGA total score was calculated by taking the mean of the erythema subscore, pustules subscore and scaling/crusting subscore. The severity of each subscore was assessed using a 5 point scale score ranging from 0 to 4 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). The final GPPGA score is assigned as follows:
- 0 , if scores for all subscores are 0,
- 1, if 0 < mean < 1.5,
- 2, if 1.5 ≤ mean < 2.5,
- 3, if 2.5 ≤ mean < 3.5,
- 4, if mean ≥ 3.5.

Randomized Set (EM−PM): This patient set includes all randomized patients.EM:primary estimand for randomised maintenance period. PM: primary method for censoring.

End point type	Primary

End point timeframe:

GPPGA was regularly assessed at baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). Patients could come to site for flare confirmation anytime as unscheduled visit. Visit window was ±7 days.

End point values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose	Spesolimab SC high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[1]	31[2]	31[3]	30[4]
Units: weeks				
median (confidence interval 95%)	37.3 (4.0 to 999999)	999999 (-999999 to 999999)	999999 (-999999 to 999999)	999999 (-999999 to 999999)

Notes:

[1] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[2] - Randomized Set (EM−PM).
-999999 and 999999= NA=Insufficient number of participants with events.
[3] - Randomized Set (EM−PM).
-999999 and 999999= NA=Insufficient number of participants with events.
[4] - Randomized Set (EM−PM).
-999999 and 999999= NA=Insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 4 different plausible dose-response patterns (linear, Emax 1, Emax 2 and exponential) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo v Spesolimab SC low dose v Spesolimab SC medium dose v Spesolimab SC high dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.002
Method	MCP-Mod linear model fit
Parameter estimate	Multiple contrast test
Point estimate	3.041
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	-999999
upper limit	999999

Notes:

[5] - The generalized MCP-Mod procedure for time to event endpoints is based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare.

Model assumption: Dose effect is linear with the increase of dose.

-999999 and 999999= Not applicable=No confidence interval applicable for this analysis.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 4 different plausible dose-response patterns (linear, Emax 1, Emax 2 and exponential) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo v Spesolimab SC low dose v Spesolimab SC medium dose v Spesolimab SC high dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.002
Method	MCP-Mod Emax2 model fit
Parameter estimate	Multiple contrast test
Point estimate	3.033

Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	-999999
upper limit	999999

Notes:

[6] - The generalized MCP-Mod procedure for time to event endpoints is based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare.

Model assumption: 95% of the maximum effect is achieved at low dose.
-999999 and 999999= Not applicable=No confidence interval for this analysis

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 4 different plausible dose-response patterns (linear, Emax 1, Emax 2 and exponential) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo v Spesolimab SC low dose v Spesolimab SC medium dose v Spesolimab SC high dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.002
Method	MCP-Mod Emax1 model fit
Parameter estimate	Multiple contrast test
Point estimate	3.088
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	-999999
upper limit	999999

Notes:

[7] - The generalized MCP-Mod procedure for time to event endpoints is based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare.

Model assumption: 70% of the maximum effect is achieved at low dose.
-999999 and 999999= Not applicable=No confidence interval for this analysis

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of spesolimab and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 4 different plausible dose-response patterns (linear, Emax 1, Emax 2 and exponential) while protecting the overall probability of type I error (one-sided alpha of 0.05).

Comparison groups	Placebo v Spesolimab SC low dose v Spesolimab SC medium dose v Spesolimab SC high dose
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.003
Method	MCP-Mod exponential model fit
Parameter estimate	Multiple contrast test
Point estimate	2.977

Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	-999999
upper limit	999999

Notes:

[8] - The generalized MCP-Mod procedure for time to event endpoints is based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare.

Model assumption: 35% of the maximum effect is achieved at medium dose.
-999999 and 999999= Not applicable=No confidence interval for this analysis

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Hazard ratio and its 95% CI (confidence interval) are from Cox regression model stratified by use of systemic GPP medication at randomisation.

Comparison groups	Placebo v Spesolimab SC medium dose
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0269 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.468
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.206
upper limit	1.064

Notes:

[9] - Null hypothesis: Effect of spesolimab 300 mg every 12 weeks on prolonging the time to the first GPP flare up to week 48 ≤ Placebo.
[10] - One-sided p−value was computed from the log−rank test stratified by use of systemic GPP medication at randomisation.
Threshold for statistical significance: one-sided p-value ≤ 0.01875.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Hazard ratio and its 95% CI (confidence interval) are from Cox regression model stratified by use of systemic GPP medication at randomisation.

Comparison groups	Placebo v Spesolimab SC high dose
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0005 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.541

Notes:

[11] - Null hypothesis: Effect of spesolimab 300 mg every 4 weeks on prolonging the time to the first GPP flare up to week 48 ≤ Placebo.
[12] - One-sided p−value is computed from the log−rank test stratified by use of systemic GPP medication at randomisation.
Threshold for statistical significance: One-sided p-value ≤0.0125.

Secondary: Key secondary endpoint: The occurrence of at least one Generalized Pustular Psoriasis (GPP) flare up to Week 48

End point title	Key secondary endpoint: The occurrence of at least one Generalized Pustular Psoriasis (GPP) flare up to Week 48

End point description:

Proportion of patients with at least one GPP flare up to Week 48 is reported. Proportions were rounded up to three decimal places.
A GPP flare was defined as increase in GPP Physician Global Assessment (GPPGA) score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2. Any use of rescue medication, or investigator-prescribed SoC for GPP worsening, prior to week 48 was considered to represent the onset of a GPP flare.
GPPGA relied on the clinical assessment of GPP patient's skin presentation. The total score is calculated by taking the mean of the three subscores: 1) erythema; 2) pustules and 3) scaling/crusting which were assessed using a scale score 0 to 4 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). The final GPPGA score:
0 , if scores of three subscores are 0,
1, if 0 < mean < 1.5;
2, if 1.5 ≤ mean < 2.5;
3, if 2.5 ≤ mean < 3.5;
4, if mean ≥ 3.5.
Randomized Set (EM−MI): This patient set includes all randomized patients. MI: multiple imputation method.

End point type	Secondary

End point timeframe:

GPPGA was regularly assessed at baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). Patients could come to site for flare confirmation anytime as unscheduled visit. Visit window was ±7 days.

End point values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose	Spesolimab SC high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[13]	31[14]	31[15]	30[16]
Units: proportion of patients				
number (confidence interval 95%)	0.516 (0.348 to 0.680)	0.226 (0.114 to 0.398)	0.297 (0.181 to 0.445)	0.127 (0.050 to 0.289)

Notes:

[13] - Randomized Set (EM−MI).

[14] - Randomized Set (EM−MI).

[15] - Randomized Set (EM−MI).

[16] - Randomized Set (EM−MI).

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Risk difference=Spesolimab high dose-Placebo.

Comparison groups	Placebo v Spesolimab SC high dose

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0013 [18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.621
upper limit	-0.159

Notes:

[17] - Null hypothesis: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 300 mg every 4 weeks ≤ Placebo.
[18] - One-sided p-value was computed from the Cochran−Mantel−Haenszel test stratified by use of systemic GPP medication at randomisation.
one-sided alpha= 0.00625

Secondary: Time to first worsening of Dermatology Quality of Life Index (DLQI) up to Week 48

End point title	Time to first worsening of Dermatology Quality of Life Index (DLQI) up to Week 48

End point description:

Worsening of DLQI up to week 48 was defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC for GPP worsening, was considered as onset of a worsening.
The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. Response categories include "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 (no effect on patient's life) to 30 (extremely large effect on patient's life).
Randomized Set (EM−PM): This patient set includes all randomized patients. EM:primary estimand for randomised maintenance period. PM: primary method for censoring.

End point type	Secondary

End point timeframe:

DLQI assessments were performed at: Baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 24, 36 and 48). Visit window was ±7 days. Time window for Week 48 was from Week 46 to Week 50.

End point values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose	Spesolimab SC high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[19]	31[20]	31[21]	30[22]
Units: weeks				
median (confidence interval 95%)	16.0 (4.0 to 999999)	35.8 (8.1 to 999999)	49.3 (8.7 to 49.3)	999999 (-999999 to 999999)

Notes:

[19] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[20] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[21] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.

[22] - Randomized Set (EM−PM).
-999999 and 999999= NA=Insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio and its 95% CI (confidence interval) are from Cox regression model stratified by use of systemic GPP medication at randomisation.
one-sided alpha= 0.00625

spesolimab high dose vs. Placebo

Comparison groups	Placebo v Spesolimab SC high dose
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.001 [24]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.259
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.62

Notes:

[23] - Null hypothesis: Effect of BI 655130 300 mg every 4 weeks on prolonging the time to the first worsening of DLQI up to week 48 ≤ Placebo.
[24] - One sided p−value was computed from the log−rank test stratified by use of systemic GPP medication at randomisation.

Secondary: Time to first worsening of Psoriasis Symptom Scale (PSS) up to Week 48

End point title	Time to first worsening of Psoriasis Symptom Scale (PSS) up to Week 48

End point description:

Worsening of Psoriasis Symptom Scale (PSS) was defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC for GPP worsening, was considered as onset of a worsening.
The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of 4 psoriasis symptoms in patients with moderate to severe psoriasis.
The symptoms included are: pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 (no symptoms) to 16 (severe symptoms)).

Randomized Set (EM−PM): This patient set includes all randomized patients. EM:primary estimand for randomised maintenance period. PM: primary method for censoring.

End point type	Secondary

End point timeframe:

PSS assessments were performed at: Baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). Visit window was ±7 days.

End point values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose	Spesolimab SC high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[25]	31[26]	31[27]	30[28]
Units: weeks				
median (confidence interval 95%)	16.0 (4.0 to 999999)	999999 (8.1 to 999999)	999999 (8.7 to 999999)	999999 (12.0 to 999999)

Notes:

[25] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[26] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[27] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.
[28] - Randomized Set (EM−PM).
999999= NA=Insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio and its 95% CI (confidence interval) are from Cox regression model stratified by use of systemic GPP medication at randomisation.

spesolimab high dose vs. Placebo

Comparison groups	Placebo v Spesolimab SC high dose
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0134 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.197
upper limit	0.914

Notes:

[29] - Null hypothesis: Effect of BI 655130 300 mg every 4 weeks on prolonging the time to first worsening of PSS up to week 48 ≤ Placebo.
[30] - One-sided p−value was computed from the log−rank test stratified by use of systemic GPP medication at randomisation.
one-sided alpha= 0.00625

Secondary: Sustained remission

End point title	Sustained remission

End point description:

Proportion of patients with sustained remission at all visits up to Week 48. Proportions were rounded up to three decimal places.
Remission was defined as a patient with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to week 48, without intake of rescue medication, or investigator-prescribed SoC for GPP worsening.
GPPGA relied on clinical assessment of GPP patient's skin presentation. The GPPGA total score was calculated by taking the mean of the erythema subscore, pustules subscore and scaling/crusting subscore. The severity of each subscore was assessed using a 5 point scale score ranging from 0 to 4 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe). The final GPPGA score is assigned as follows:
- 0 , if scores of three subscores are 0,
- 1, if 0 < mean < 1.5,
- 2, if 1.5 ≤ mean < 2.5,

- 3, if 2.5 ≤ mean < 3.5,
- 4, if mean ≥ 3.5.
Randomized Set (EM−MI): This patient set includes all randomized patients. MI: multiple imputation method.

End point type	Secondary

End point timeframe:

GPPGA was regularly assessed at baseline (Week 1) and up to Week 48 (at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). Patients could come to site for flare confirmation anytime as unscheduled visit. Visit window was ±7 days.

End point values	Placebo	Spesolimab SC low dose	Spesolimab SC medium dose	Spesolimab SC high dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31[31]	31[32]	31[33]	30[34]
Units: proportion of patients				
number (confidence interval 95%)	0.290 (0.161 to 0.466)	0.516 (0.348 to 0.680)	0.452 (0.292 to 0.622)	0.633 (0.471 to 0.770)

Notes:

[31] - Randomized Set (EM−MI).

[32] - Randomized Set (EM−MI).

[33] - Randomized Set (EM−MI).

[34] - Randomized Set (EM−MI).

Statistical analyses

No statistical analyses for this end point

Secondary: The occurrence of treatment emergent adverse events (TEAEs)

End point title	The occurrence of treatment emergent adverse events

End point description:

Percentage of patients with treatment emergent adverse events (TEAEs) is reported. Percentages were rounded up to one decimal places.

Time Frame: Placebo, Spesolimab (Speso) SC low, medium, high: From randomized study treatment start until the first use of rescue medication with IV spesolimab or until last dose + 16 weeks, up to 62 weeks.
Speso IV SD and Speso IV DD: From first use of rescue medication with IV spesolimab until OL maintenance spesolimab SC or until last dose of spesolimab IV + 16 weeks, up to 17 weeks.
Speso OL SC: From the first dose of OL spesolimab SC treatment until last dose 16 weeks, up to 62 weeks.

Arms "Placebo, Speso SC Low, medium, high":Safety Set (SAF)-This patient set included all patients who were randomized and received at least one dose of study drug.
Arms "Speso IV SD, Speso IV DD": SAF-FT- Safety Analysis set for flare rescue treatment period.
Arm "Speso OL SC": SAF-MT- Safety Analysis set for OL maintenance treatment period.

End point type	Secondary

End point timeframe:

Up to 62 weeks (for detailed timeframe see description).

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm "Spesolimab SC low dose" is reported as a Subject Analysis Set, because it includes also on patient from the Placebo arm. The patients from the placebo arm was randomized to “Placebo” arm but received active spesolimab dose, therefore is reported under the arm "Spesolimab SC low dose".

End point values	Spesolimab SC medium dose	Spesolimab SC high dose	Spesolimab IV SD	Spesolimab IV DD
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	31	30	22	10
Units: percentage of patients				
number (not applicable)	93.5	86.7	68.2	60.0

End point values	Spesolimab OL SC	Spesolimab SC low dose (safety)	Placebo (safety)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	32	30	
Units: percentage of patients				
number (not applicable)	75.0	90.6	86.7	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Up to 62 weeks (for detailed timeframe please see the description of the endpoint "The occurrence of treatment emergent adverse events (TEAEs)").

Adverse event reporting additional description:

Placebo, Speso SC Low, medium, high":Safety Set (SAF). One patient who was randomized to placebo arm but received active spesolimab dose is reported under the arm "Spesolimab SC low".
"Speso IV SD and DD": SAF-FT- Safety Analysis set for flare rescue treatment period.
"Speso OL SC": SAF-MT- Safety Analysis set for OL maintenance treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients were subcutaneously (SC) injected on Day 1 of Week 1 a loading dose of solution for injection of placebo matching solution for injection of spesolimab followed by a maintenance tretament which consisted of a subcutaneous injection of solution for injection of placebo matching solution for injection of spesolimab every 4 weeks (i.e. on Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44).
The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 of flare (R1/D1) or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Speso SC low dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of two subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300mg) and two subcutaneous injections of placebo matching solution for injection of spesolimab. The loading dose was followed by a maintenance treatment which consisted of one SC injection of 150 mg of solution for injection of spesolimab and one SC injection of placebo matching solution for injection of spesolimab every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at R1/D1 of flare or at R1/D1 and at R3/D8 of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Speso SC medium dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 12 weeks (i.e. at Week 12, 24 and 36). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of 300 mg of spesolimab administered subcutaneously every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Speso SC high dose

Reporting group description:

Patients received on Day 1 of Week 1 a loading dose which consisted of four subcutaneous (SC) injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab= 600 mg). The loading dose was followed by a maintenance treatment which consisted of two SC injections of 150 mg of solution for injection of spesolimab (total dose of spesolimab=300 mg) every 4 weeks (i.e. at Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44). The patients who experienced a flare during the 48 week randomised treatment period were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare followed by OL maintenance treatment if time allowed which consisted of

300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Reporting group title	Speso IV SD

Reporting group description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who took a single dose (SD) of rescue treatment of 900 milligram (mg) of spesolimab administered intravenously (IV) at Day 1 of flare (R1/D1) because of a GPP flare during the 48 week treatment randomised period.

Reporting group title	Speso IV DD

Reporting group description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who took two doses (DD) of rescue treatment of spesolimab each 900 milligram (mg) of spesolimab administered intravenously (IV) at Day 1 and at Day 8 of flare (R1/D1 and R3/D8) because of a GPP flare during the 48 week treatment randomised period.

Reporting group title	Speso OL SC

Reporting group description:

This arm includes the patients who were randomized at study start in the arms "Placebo" or "Spesolimab SC low dose" or "Spesolimab SC medium dose" or "Spesolimab SC high dose" who experienced a flare during the 48 week randomised treatment period and were administered intravenously (IV) in an open label (OL) fashion with 900 milligram (mg) of solution for infusion of spesolimab at either Day 1 (R1/D1) of flare or at Day 1 (R1/D1) and at Day 8 (R3/D8) of flare and then followed by maintenance treatment which consisted of 300 mg of spesolimab administered SC every 12 weeks or every 4 weeks (intensified maintenance therapy).

Serious adverse events	Placebo	Speso SC low dose	Speso SC medium dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)	5 / 32 (15.63%)	1 / 31 (3.23%)
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 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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			
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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			
Multiple sclerosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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			
Cholelithiasis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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			
Angioedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Drug eruption			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Pustular psoriasis			

subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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
Encephalitis viral			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (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
Septic shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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 bacterial infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (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

Serious adverse events	Speso SC high dose	Speso IV SD	Speso IV DD
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 30 (10.00%)	1 / 22 (4.55%)	4 / 10 (40.00%)
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 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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	1 / 30 (3.33%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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			
Multiple sclerosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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
Hypertensive encephalopathy			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	1 / 30 (3.33%)	0 / 22 (0.00%)	0 / 10 (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			
Angioedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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
Drug eruption			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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	1 / 30 (3.33%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis viral			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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
Pneumonia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin bacterial infection			

subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (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
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 22 (4.55%)	0 / 10 (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

Serious adverse events	Speso OL SC		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive encephalopathy			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug eruption			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pustular psoriasis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis viral			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin bacterial infection			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Speso SC low dose	Speso SC medium dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 30 (80.00%)	25 / 32 (78.13%)	23 / 31 (74.19%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 30 (6.67%)	4 / 32 (12.50%)	1 / 31 (3.23%)
occurrences (all)	3	5	1
Tryptase increased			

subjects affected / exposed	0 / 30 (0.00%)	3 / 32 (9.38%)	0 / 31 (0.00%)
occurrences (all)	0	5	0
Protein urine present			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Blood trypsin increased			
subjects affected / exposed	1 / 30 (3.33%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	1	6	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 30 (3.33%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	2	1	2
Injection site swelling			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)	3 / 32 (9.38%)	2 / 31 (6.45%)
occurrences (all)	1	3	2
Injection site induration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			

subjects affected / exposed	1 / 30 (3.33%)	4 / 32 (12.50%)	4 / 31 (12.90%)
occurrences (all)	1	16	6
Gastrointestinal disorders			
Odynophagia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 30 (6.67%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	3	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 32 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
Erythema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Psoriasis			
subjects affected / exposed	3 / 30 (10.00%)	4 / 32 (12.50%)	5 / 31 (16.13%)
occurrences (all)	3	4	6
Pustular psoriasis			
subjects affected / exposed	16 / 30 (53.33%)	9 / 32 (28.13%)	9 / 31 (29.03%)
occurrences (all)	16	9	10
Seborrhoeic dermatitis			

subjects affected / exposed	1 / 30 (3.33%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences (all)	1	2	2
Urticaria			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	1 / 31 (3.23%)
occurrences (all)	4	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	4 / 32 (12.50%)	1 / 31 (3.23%)
occurrences (all)	1	4	2
Joint swelling			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 30 (3.33%)	2 / 32 (6.25%)	1 / 31 (3.23%)
occurrences (all)	1	2	1
Folliculitis			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
Influenza			
subjects affected / exposed	0 / 30 (0.00%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 32 (3.13%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 30 (13.33%)	3 / 32 (9.38%)	6 / 31 (19.35%)
occurrences (all)	5	5	8
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	1 / 32 (3.13%)	3 / 31 (9.68%)
occurrences (all)	2	1	4
Metabolism and nutrition disorders			

Hypertriglyceridaemia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 32 (6.25%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Hyperlipidaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 32 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Speso SC high dose	Speso IV SD	Speso IV DD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 30 (66.67%)	12 / 22 (54.55%)	3 / 10 (30.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tryptase increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood trypsin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 22 (4.55%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 30 (3.33%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	2 / 30 (6.67%)	2 / 22 (9.09%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Injection site swelling			

subjects affected / exposed	1 / 30 (3.33%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)	2 / 22 (9.09%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Injection site induration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injection site erythema			
subjects affected / exposed	5 / 30 (16.67%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	17	0	0
Gastrointestinal disorders			
Odynophagia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 22 (4.55%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Dermatitis contact			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 30 (3.33%)	2 / 22 (9.09%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Pruritus			
subjects affected / exposed	2 / 30 (6.67%)	1 / 22 (4.55%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Psoriasis			
subjects affected / exposed	4 / 30 (13.33%)	1 / 22 (4.55%)	1 / 10 (10.00%)
occurrences (all)	5	1	1
Pustular psoriasis			
subjects affected / exposed	2 / 30 (6.67%)	5 / 22 (22.73%)	0 / 10 (0.00%)
occurrences (all)	2	6	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 30 (10.00%)	2 / 22 (9.09%)	0 / 10 (0.00%)
occurrences (all)	5	3	0
Joint swelling			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 30 (10.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0

Folliculitis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 22 (4.55%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	1 / 30 (3.33%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	4 / 30 (13.33%)	2 / 22 (9.09%)	1 / 10 (10.00%)
occurrences (all)	6	2	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 22 (4.55%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 22 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Speso OL SC		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Tryptase increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Protein urine present			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Blood trypsin increased			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		
Injection site swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Injection site induration			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Chest discomfort			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	6		
Gastrointestinal disorders			
Odynophagia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Psoriasis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pustular psoriasis			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2020	Global Amendment No. 1: Changes to Section 7, no longer monitoring the event rate, since it is expected that sufficient events would be observed in the target population. Changes to Section 7.4, changes to randomization to make sure adolescents were included in each treatment arm.
19 April 2021	Global Amendment No. 2: Changes to Section 7.2.2, to align with Pediatric Investigational Plan (PIP). Changes to Section 7.2.3, descriptive analysis of adults vs pediatric patients to align with PIP. Changes to Section 4.1.4 to permit home administration of treatment drug, if necessary, due to COVID-19.
28 July 2022	Global Amendment No. 3: Changes to Section 5.2.6.1.4, to include peripheral neuropathy as an adverse event of special interest. Changes to Section 4.2.2.2, to allow the investigator to determine if a patient should continue rescue therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported