



Clinical trial results:

Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of spesolimab (BI 655130) in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity

Summary

EudraCT number	2017-004231-37
Trial protocol	FR DE
Global end of trial date	05 January 2021

Results information

Result version number	v2 (current)
This version publication date	01 March 2022
First version publication date	11 January 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1368-0013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03782792
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	01 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2020
Global end of trial reached?	Yes
Global end of trial date	05 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy, tolerability, and safety of spesolimab (BI 655130) compared with placebo in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.

Protection of trial subjects:

Week1/Day 2 to D7:

- If the severity and progression of the disease worsened within the 1st week and required immediate treatment, then the investigator could treat the patient with the escape medication of his/her choice.

After Day 8:

- Patients who did not achieve a clinical response (Generalized Pustular Psoriasis Physician Global Assessment 0 or 1) but had disease worsening subsequent to Day 8 could receive an escape treatment chosen by the investigator

- Patients who achieved a clinical response and later had disease worsening that was not severe enough to meet the criteria for recurrence for Generalized Pustular Psoriasis (GPP) flare could receive the escape medication. However, it was recommended to wait until the patient met the criteria for recurrence of GPP flare since there was an option to administer rescue medication with Open Label spesolimab instead at this time.

Patients were allowed to withdraw their consent at any time without the need to justify the decision.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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	China: 9
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Malaysia: 20
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Thailand: 1

Country: Number of subjects enrolled	Tunisia: 9
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	85
EEA total number of subjects	24

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)	79
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, placebo-controlled, double-blind, parallel-group, single-dose trial with 2 treatment groups (spesolimab and placebo) in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.

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

Blinding implementation details:

Patients and investigators involved in the trial conduct remained blinded with regard to the randomized treatment assignments until after database lock for the final trial analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients received intravenously (i.v.) solution for infusion containing 900 mg of placebo to spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received intravenously (i.v.) solution for infusion containing 900 milligram (mg) of placebo to spesolimab on Day 1 (D1) of Week 1 (Wk1).

Arm title	Spesolimab 900 mg i.v SD
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Arm description:

Patients received intravenously (i.v.) a single dose (SD) of solution for infusion containing 900 milligram (mg) of spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single

rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.

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

Dosage and administration details:

Patients received intravenously (i.v.) a single dose (SD) of solution for infusion containing 900 milligram (mg) of spesolimab on Day 1 (D1) of Week 1 (Wk1).

Number of subjects in period 1^[1]	Placebo	Spesolimab 900 mg i.v SD
Started	18	35
Received OL Spesolimab at Wk1/D8	15 ^[2]	12 ^[3]
Received rescue Spesolimab after Wk1	2 ^[4]	4 ^[5]
Completed	17	32
Not completed	1	3
Consent withdrawn by subject	1	2
Patient left the country	-	1

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: 85 patients were screened, of whom 53 were randomised.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of 18 subjects that were treated with Placebo on Day 1 only 2 received rescue Spesolimab after Week 1.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of 35 subjects that were treated with Spesolimab 900 mg i.v on Day 1 only 12 received Open Label Spesolimab at Week 1/Day 8.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of 18 subjects that were treated with Placebo on Day 1 only 15 received Open Label Spesolimab at Week 1/Day 8.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of 35 subjects that were treated with Spesolimab 900 mg i.v on Day 1 only 4 received rescue Spesolimab after Week 1.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients received intravenously (i.v.) solution for infusion containing 900 mg of placebo to spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.	
Reporting group title	Spesolimab 900 mg i.v SD
Reporting group description:	
Patients received intravenously (i.v.) a single dose (SD) of solution for infusion containing 900 milligram (mg) of spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.	

Reporting group values	Placebo	Spesolimab 900 mg i.v SD	Total
Number of subjects	18	35	53
Age categorical			
Randomized Set (RS): This patient set included 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)	0	0	0
Adults (18-64 years)	18	33	51
From 65-84 years	0	2	2
85 years and over	0	0	0
Age Continuous			
Randomized Set (RS): This patient set included all randomized patients.			
Units: years			
arithmetic mean	42.6	43.2	
standard deviation	± 8.4	± 12.1	-
Sex: Female, Male			
Randomized Set (RS): This patient set included all randomized patients.			
Units: Participants			
Female	15	21	36
Male	3	14	17

Race (NIH/OMB)			
Randomized Set (RS): This patient set included all randomized patients.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	13	16	29
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	19	24
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomized Set (RS): This patient set included all randomized patients.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	18	35	53
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients received intravenously (i.v.) solution for infusion containing 900 mg of placebo to spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.	
Reporting group title	Spesolimab 900 mg i.v SD
Reporting group description:	
Patients received intravenously (i.v.) a single dose (SD) of solution for infusion containing 900 milligram (mg) of spesolimab on Day 1 (D1) of Week 1 (Wk1). If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there was an option to administer open label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.	

Primary: Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 indicating no visible pustules at Week 1

End point title	Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 indicating no visible pustules at Week 1
End point description:	
The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) relies on clinical assessment of the Generalized Pustular Psoriasis (GPP) patient's skin presentation. The investigator (or qualified site personnel) scored the erythema, pustules, and scaling of all GPP lesions from 0 to 4. The GPPGA pustulation subscore ranges from 0 to 4 where: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. A lower GPPGA pustulation subscore indicates a better outcome. A GPPGA pustulation subscore of 0 means no visible pustules. The proportion of patients who achieved a GPPGA pustulation subscore of 0 at Week 1 is reported. Randomized Set (RS) (via estimand EN-NRI): EN = Any assessments after death, or any use of escape medication due to disease worsening prior to Week 1 were considered to represent a non-response. NRI = Non-response imputation for any missing data.	
End point type	Primary
End point timeframe:	
At Week 1.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[1]	35 ^[2]		
Units: Proportion of participants				
number (confidence interval 95%)	0.056 (0.010 to 0.258)	0.543 (0.382 to 0.695)		

Notes:

[1] - RS via estimand EN-NRI

[2] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The Suissa-Shuster Z-pooled test was implemented to test the treatment effect on the primary endpoint on the RS (estimand EN) at a 1-sided, alpha level of 0.025. Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.	
Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0004 ^[3]
Method	Suissa-Shuster Z-pooled test
Parameter estimate	Risk difference (RD)
Point estimate	0.487
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.672

Notes:

[3] - One-sided P Value.

Secondary: Proportion of patients with a Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4

End point title	Proportion of patients with a Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4
End point description:	
Generalized Pustular Psoriasis Area and Severity Index (GPPASI) provides a numeric scoring for a patient's overall Generalized Pustular Psoriasis (GPP) disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (head, trunk, upper limbs and lower limbs).	
A higher score indicates a worse disease state, while a score of 0 indicates no disease. GPPASI 75 is based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an 75% reduction.	
Proportion of patients with GPPASI 75 at Week 4 is reported.	
Randomized Set (RS) (via estimand EN-NRI): EN = Any assessments after death, or any use of escape medication due to disease worsening prior to Week 1 were considered to represent a non-response. NRI = Non-response imputation for any missing data.	
End point type	Secondary
End point timeframe:	
At Week 4.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[4]	35 ^[5]		
Units: Proportion of participants				
number (confidence interval 95%)	0.111 (0.031 to 0.328)	0.457 (0.305 to 0.618)		

Notes:

[4] - RS via estimand EN-NRI

[5] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

The Suissa-Shuster Z-pooled test was implemented to test the treatment effect on the RS (estimand EN) at a 1-sided, alpha level of 0.025. Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0081 ^[6]
Method	Suissa-Shuster Z-pooled test
Parameter estimate	Risk difference (RD)
Point estimate	0.346
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.554

Notes:

[6] - One-sided P Value.

Secondary: Key secondary: Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1

End point title	Key secondary: Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1
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End point description:

GPPGA relied on clinical assessment of the Generalized Pustular Psoriasis (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 three subscores are 0,
- 1, if $0 < \text{mean} < 1.5$,
- 2, if $1.5 \leq \text{mean} < 2.5$,
- 3, if $2.5 \leq \text{mean} < 3.5$,
- 4, if $\text{mean} \geq 3.5$.

A lower GPPGA score indicates a better outcome, with 0 being clear and 1 being almost clear. The proportion of patients with a GPPGA score of 0 or 1 at Week 1 is reported.

Randomized Set (RS) (via estimand EN-NRI): EN = Any assessments after death, or any use of escape

medication due to disease worsening prior to Week 1 were considered to represent a non-response. NRI = Non-response imputation for any missing data.

End point type	Secondary
End point timeframe:	
At Week 1.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[7]	35 ^[8]		
Units: Proportion of participants				
number (confidence interval 95%)	0.111 (0.031 to 0.328)	0.429 (0.280 to 0.591)		

Notes:

[7] - RS via estimand EN-NRI

[8] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The Suissa-Shuster Z-pooled test was implemented to test the treatment effect on the RS (estimand EN) at a 1-sided, alpha level of 0.025. Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0118 ^[9]
Method	Suissa-Shuster Z-pooled test
Parameter estimate	Risk difference (RD)
Point estimate	0.317
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.527

Notes:

[9] - One-sided P Value.

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

End point title	Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4
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End point description:

The Pain VAS is a participant-administered single-item scale designed to measure skin pain intensity from generalized pustular psoriasis (GPP) using a 100 millimeter (mm) horizontal VAS. Overall severity of participant's skin pain from GPP is indicated by placing a single mark on the horizontal 100 mm scale from 0 mm (no pain) to 100 mm (pain as bad as one can imagine).

Change from baseline was calculated by subtracting the VAS score at baseline from the VAS score at Week 4. A negative change indicates an improvement from baseline.

Death, any use of escape medication, OL Spesolimab at Day 8, or rescue medication with Spesolimab after Day 8, prior to observing the endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (NR).

NR is not a missing value but the worst possible outcome of the endpoint. For example, if the achieved data is (NR, NR, NR, NR, NR, NR, 2, 3, 3, 3, 5) then Q1 is NR, median is NR and Q3 is 3.
-99999 and 99999= NR

End point type	Secondary
End point timeframe:	
Baseline and at Week 4.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[10]	35 ^[11]		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	99999 (-99999 to 99999)	-22.45 (-70.41 to 99999)		

Notes:

[10] - RS-last observation carried forward (LOCF)

[11] - RS-LOCF

Statistical analyses

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

The effect of spesolimab was evaluated by a Wilcoxon rank test using the RS. Any assessments after death, the use of escape medication (before or after Day 8), open label spesolimab on Day 8, or rescue medication with spesolimab after Day 8 were assigned worst ranks for the testing. Missing data at Week 4 were imputed and handled via assessment of ranks.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012 ^[12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - One-sided P Value.

Secondary: Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4

End point title	Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
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End point description:

PSS is a 4-item patient-reported outcome instrument that assesses the severity of psoriasis symptoms in moderate to severe psoriasis patients. The symptoms included are: pain, redness, itching, and burning. The symptom severity was assessed using a 5 point scale ranging from 0 to 4 where 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. The symptom scores are added to an unweighted total score (range: 0 to 16). A lower PSS score indicates a better outcome. Change from baseline = PSS score at Week 4 - PSS score at baseline. Death, any use of escape medication, OL Spesolimab at Day 8, or rescue medication with Spesolimab after Day 8, prior to observing the endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (NR). NR is not a missing value but the worst possible outcome of the endpoint. For example, if the achieved data is (NR, NR, NR, NR, NR, NR, 2, 3, 3, 3, 5) then Q1 is NR, median is NR and Q3 is 3.
99999 and 99999= NR.

End point type	Secondary
End point timeframe:	
Baseline and at Week 4.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[13]	35 ^[14]		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	99999 (-99999 to 99999)	-2.0 (-9.0 to 99999)		

Notes:

[13] - RS via estimand EN-LOCF

[14] - RS via estimand EN-LOCF

Statistical analyses

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

The effect of spesolimab was evaluated by a Wilcoxon rank test using the RS. Any assessments after death, the use of escape medication (before or after Day 8), open label spesolimab on Day 8, or rescue medication with spesolimab after Day 8 were assigned worst ranks for the testing. Missing data at Week 4 were imputed and handled via assessment of ranks.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0044 ^[15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - One-sided P Value.

Secondary: Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue score at Week 4

End point title	Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) - Fatigue score at Week 4
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End point description:

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. Each item is scored from 0 to 4. Score range is 0 (extreme fatigue)-52 (no fatigue).

Change from baseline=FACIT Fatigue score at Week 4- FACIT-Fatigue score at baseline. Death, any use of escape medication, OL Spesolimab at Day 8, or rescue medication with Spesolimab after Day 8, prior to observing the endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (NR). NR is not a missing value but the worst possible outcome of the endpoint. For example, if the achieved data is s (NR, NR, NR, NR, NR, NR, 2, 3, 3, 3, 5) then Q1 is NR, median is NR and Q3 is 3.

RS via estimand EN-LOCF.

-99999 and 99999= NR

End point type	Secondary
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End point timeframe:

Baseline and at Week 4.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[16]	35 ^[17]		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	99999 (-99999 to 99999)	3.00 (-99999 to 30.00)		

Notes:

[16] - RS via estimand EN-LOCF

[17] - RS via estimand EN-LOCF

Statistical analyses

Statistical analysis title	Statistical Analysis 6
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Statistical analysis description:

The effect of spesolimab was evaluated by a Wilcoxon rank test using the RS. Any assessments after death, the use of escape medication (before or after Day 8), open label spesolimab on Day 8, or rescue medication with spesolimab after Day 8 were assigned worst ranks for the testing. Missing data at Week 4 were imputed and handled via assessment of ranks.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012 ^[18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - One-sided P Value.

Secondary: Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 4

End point title	Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 4
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End point description:

GPPGA relied on clinical assessment of the Generalized Pustular Psoriasis (GPP) patient's skin presentation. The GPPGA total score is 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 three scores are 0,
- 1, if $0 < \text{mean} < 1.5$,
- 2, if $1.5 \leq \text{mean} < 2.5$,
- 3, if $2.5 \leq \text{mean} < 3.5$,
- 4, if $\text{mean} \geq 3.5$.

A lower GPPGA score indicates a better outcome, with 0 being clear and 1 being almost clear. Randomized Set (RS) (via estimand EN-NRI):EN = Any assessments after death, or the use of escape medication (before or after Day 8), or open-label Spesolimab at Day 8, or rescue medication with Spesolimab after Day 8, was considered a non-response. NRI = Non-response imputation for any missing data.

End point type	Secondary
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End point timeframe:

At Week 4.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[19]	35 ^[20]		
Units: Proportion of participants				
number (confidence interval 95%)	0.111 (0.031 to 0.328)	0.486 (0.330 to 0.644)		

Notes:

[19] - RS via estimand EN-NRI

[20] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 7
Statistical analysis description:	
Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.	
Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.375
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.581

Secondary: Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score of 0 indicating no visible pustules at Week 4

End point title	Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score of 0 indicating no visible pustules at Week 4
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End point description:

The Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) relies on clinical assessment of the Generalized Pustular Psoriasis (GPP) patient's skin presentation. The investigator (or qualified site personnel) scores the erythema, pustules, and scaling of all GPP lesions from 0 to 4.

The GPPGA pustulation subscore ranges from 0 to 4 where:

0 = clear;

1 = almost clear;

2 = mild;

3 = moderate;

4 = severe.

A lower GPPGA pustulation subscore indicates a better outcome.

Randomized Set (RS) (via estimand EN-NRI): EN = Any assessments after death, or the use of escape medication (before or after Day 8), or open-label spesolimab at Day 8, or rescue medication with spesolimab after Day 8, was considered a non-response. NRI = Non-response imputation for any missing data.

End point type	Secondary
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End point timeframe:

At Week 4.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[21]	35 ^[22]		
Units: Proportion of participants				
number (confidence interval 95%)	0.111 (0.031 to 0.328)	0.514 (0.356 to 0.670)		

Notes:

[21] - RS via estimand EN-NRI

[22] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.	
Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.607

Secondary: Proportion of patients with a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) 50 at Week 4

End point title	Proportion of patients with a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) 50 at Week 4
End point description:	
Generalized Pustular Psoriasis Area and Severity Index (GPPASI) provides a numeric scoring for a patient's overall Generalized Pustular Psoriasis (GPP) disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (head, trunk, upper limbs and lower limbs).	
A higher score indicates a worse disease state, while a score of 0 indicates no disease. GPPASI 50 is based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an 50 % reduction.	
Randomized Set (RS) (via estimand EN-NRI):EN = Any assessments after death, or the use of escape medication (before or after Day 8), or open-label spesolimab at Day 8, or rescue medication with spesolimab after Day 8, was considered a non-response. NRI = Non-response imputation for any missing data.	
End point type	Secondary
End point timeframe:	
At Week 4.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[23]	35 ^[24]		
Units: Proportion of participants				
number (confidence interval 95%)	0.111 (0.031 to 0.328)	0.543 (0.382 to 0.695)		

Notes:

[23] - RS via estimand EN-NRI

[24] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.	
Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.432
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.636

Secondary: Percent change in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) from baseline at Week 4

End point title	Percent change in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) from baseline at Week 4
End point description:	
<p>GPPASI provides a numeric scoring for a patient's overall Generalized Pustular Psoriasis (GPP) disease state, ranging from 0 (no disease) to 72 (worse disease state). It is a linear combination of percent of surface area of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (head, trunk, upper limbs and lower limbs).</p> <p>%GPPASI change from baseline=(GPPASI at Week 4-GPPASI at baseline) *100/(GPPASI at baseline).</p> <p>Death, any use of escape medication, OL Spesolimab at Day 8, or rescue medication with Spesolimab after Day 8, prior to observing the endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (NR). NR is not a missing value but the worst possible outcome of the endpoint. For example, if the achieved data is (NR, NR, NR, NR, NR, NR, 2, 3, 3, 3, 5) then Q1 is NR, median is NR and Q3 is 3.</p> <p>RS via estimand EN-LOCF.</p> <p>-99999 and 99999= Non- response</p>	
End point type	Secondary
End point timeframe:	
Baseline and at Week 4.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[25]	35 ^[26]		
Units: Percentage change				
median (inter-quartile range (Q1-Q3))	99999 (-99999 to 99999)	-60.50 (-88.37 to 99999)		

Notes:

[25] - RS via estimand EN-LOCF

[26] - RS via estimand EN-LOCF

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) 50 at Week 1

End point title	Proportion of patients with a Generalized Pustular Psoriasis Area and Severity Index (GPPASI) 50 at Week 1
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End point description:

Generalized Pustular Psoriasis Area and Severity Index (GPPASI) provides a numeric scoring for a patient's overall Generalized Pustular Psoriasis (GPP) disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (head, trunk, upper limbs and lower limbs).

A higher score indicates a worse disease state, while a score of 0 indicates no disease. GPPASI 50 is based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an 50 % reduction.

Randomized Set (RS) (via estimand EN-NRI).

End point type	Secondary
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End point timeframe:

At Week 1.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[27]	35 ^[28]		
Units: Proportion of participants				
number (confidence interval 95%)	0.278 (0.125 to 0.509)	0.429 (0.280 to 0.591)		

Notes:

[27] - RS via estimand EN-NRI

[28] - RS via estimand EN-NRI

Statistical analyses

Statistical analysis title	Statistical Analysis 10
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Statistical analysis description:

Confidence intervals (95%) around the risk difference were produced using the Chan and Zhang method.

Comparison groups	Placebo v Spesolimab 900 mg i.v SD
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.138
upper limit	0.401

Secondary: Percent change in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) from baseline at Week 1

End point title	Percent change in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) from baseline at Week 1
End point description:	
<p>Generalized Pustular Psoriasis Area and Severity Index (GPPASI) provides a numeric scoring for a patient's overall Generalized Pustular Psoriasis (GPP) disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin affected by erythema, pustules, and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions (head, trunk, upper limbs and lower limbs).</p> <p>A higher score indicates a worse disease state, while a score of 0 indicates no disease.</p> <p>The percent change from baseline at Week 1 is calculated as:</p> <p>% GPPASI change from baseline = (GPPASI at Week 1 - GPPASI at baseline) *100/GPPASI at baseline.</p> <p>If % GPPASI change from baseline is positive, it means the disease is becoming worse.</p> <p>Randomized Set (RS) via estimand EN-LOCF.</p>	
End point type	Secondary
End point timeframe:	
At Week 1.	

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[29]	35 ^[30]		
Units: Percentage change				
median (inter-quartile range (Q1-Q3))	1.02 (-60.47 to 36.68)	-42.80 (-69.84 to 9.49)		

Notes:

[29] - RS via estimand EN-LOCF

[30] - RS via estimand EN-LOCF

Statistical analyses

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
<p>Any assessments after death, the use of escape medication (before or after Day 8), open label spesolimab on Day 8, or rescue medication with spesolimab after Day 8 and assigned with the worst possible outcomes in rank analysis. Missing data at Week 4 were imputed and handled via assessment of ranks.</p>	
Comparison groups	Placebo v Spesolimab 900 mg i.v SD

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Median difference (final values)
Point estimate	-16.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.32
upper limit	12.76

Secondary: Occurrence of Treatment Emergent Adverse Events (TEAEs) up to Week 1

End point title	Occurrence of Treatment Emergent Adverse Events (TEAEs) up to Week 1
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End point description:

TEAEs were all Adverse Events (AEs) occurring between start of treatment and Day 8 (Day 8 excluded). AEs that started before first drug intake and deteriorated under treatment were also considered as 'treatment-emergent'.

The exposure-adjusted incidence rate was calculated as:

Incidence rate [1/100 patients-years] = $100 \times \text{number of patients with AE} / \text{Total AE specific time at risk [patient-years]}$

where: Time at risk [patient-years] = (date of onset of TEAE – study drug start date + 1) / 365.25

Safety Analysis set (SAF): This patient set included all patients who were randomized and received at least one dose of study drug on Day 1. Patients were analyzed according to the actual treatment received.

End point type	Secondary
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End point timeframe:

From start of treatment until Day 7, up to 7 days.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[31]	35 ^[32]		
Units: events per 100 patient-years at risk				
number (not applicable)	6445.6	8650.7		

Notes:

[31] - SAF

[32] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Treatment Emergent Adverse Events (TEAEs) up to Week 1

End point title	Number of patients with Treatment Emergent Adverse Events (TEAEs) up to Week 1
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End point description:

TEAEs were all Adverse Events (AEs) occurring between start of treatment and Day 8 (Day 8 excluded). AEs that started before first drug intake and deteriorated under treatment were also considered as 'treatment-emergent'.

Safety Analysis set (SAF): This patient set included all patients who were randomized and received at least one dose of study drug on Day 1. Patients were analyzed according to the actual treatment received.

End point type	Secondary
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End point timeframe:

From start of treatment until Day 7, up to 7 days.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[33]	35 ^[34]		
Units: Participants	12	27		

Notes:

[33] - SAF

[34] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Treatment Emergent Adverse Events (TEAEs) within the treatment phase

End point title	Occurrence of Treatment Emergent Adverse Events (TEAEs) within the treatment phase
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End point description:

TEAEs were all Adverse Events (AEs) occurring between start of treatment and end of the residual effect period (REP) (16 weeks). AEs that started before first drug intake and deteriorated under treatment were also considered as 'treatment-emergent'.

The exposure-adjusted incidence rate was calculated as:

Incidence rate [1/100 patients-years] = $100 \times \text{number of patients with AE} / \text{Total AE specific time at risk [patient-years]}$

where Time at risk

where: Time at risk [patient-years] = (date of onset of TEAE – study drug start date + 1) / 365.25

If, for a patient, the selected TEAE did not occur then the time at risk was censored at min

- Date of death

- For patients who did not roll over into the Open Label Extension (OLE) study: last contact date Visit14/15

- For patients who rolled over into the OLE study: the 1st dose in the OLE study

- Drug stop date + 112 days

- Date of Day 8 if OL spesolimab was given

- Date of rescue medication if spesolimab was given.

End point type	Secondary
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End point timeframe:

From start of treatment until end of the residual effect period (REP) but censored at any use of open label spesolimab, up to 16 weeks.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[35]	35 ^[36]		
Units: events per 100 patient-years at risk				
number (not applicable)	3083.3	2391.0		

Notes:

[35] - SAF.

[36] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Treatment Emergent Adverse Events (TEAEs) within the treatment phase

End point title	Number of patients with Treatment Emergent Adverse Events (TEAEs) within the treatment phase
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End point description:

TEAEs were all Adverse Events (AEs) occurring between start of treatment and end of the residual effect period (REP) (16 weeks). AEs that started before first drug intake and deteriorated under treatment were also considered as 'treatment-emergent'.

Safety Analysis set (SAF): This patient set included all patients who were randomized and received at least one dose of study drug on Day 1. Patients were analyzed according to the actual treatment received.

End point type	Secondary
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End point timeframe:

From start of treatment until end of the residual effect period (REP) but censored at any use of open label spesolimab, up to 16 weeks.

End point values	Placebo	Spesolimab 900 mg i.v SD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18 ^[37]	35 ^[38]		
Units: Participants	13	29		

Notes:

[37] - SAF

[38] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo and Spesolimab 900 mg i.v. SD arms: From the start of infusion of randomized medication at Day 1 (D1) of Week 1 (Wk1) until the end of its REP (16 weeks) but were censored at any use of open-label (OL) spesolimab.

Adverse event reporting additional description:

Safety Analysis set (SAF)

OL Spesolimab: From the start of OL spesolimab at Wk1/D8 until the end of its REP (16 weeks) but were censored at any use of rescue medication with spesolimab.

Rescue Spesolimab: From the start of rescue medication with spesolimab until the end of its REP (16 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Patients received intravenously (i.v.) solution for infusion containing 900 mg of placebo to spesolimab on Day 1 (D1) of Week 1 (Wk1). Based on the subsequent treatment response, participants were then to be followed up for 12 to 28 weeks. If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing SoC since there was an option to administer open label (OL) spesolimab instead at this time. If SoC was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8. If the condition of the patients worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab after Wk1 to Wk 12.

Reporting group title	Rescue Spesolimab 900 mg i.v.
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Reporting group description:

This arm included patients who in addition to the randomized treatment (either intravenously (i.v.) placebo solution to spesolimab at Day 1 or 900 milligram (mg) i.v. spesolimab at Day 1) also one single rescue i.v. dose of 900 mg spesolimab between Week 1(Wk 1) to Week 12 (Wk 12).

Reporting group title	Open Label (OL) D8 Spesolimab 900 mg i.v.
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Reporting group description:

This arm included patients who in addition to the randomized treatment (either intravenously (i.v.) placebo solution to spesolimab at Day 1 or 900 milligram (mg) i.v. spesolimab at Day 1) received also Open Label Treatment with 900 mg I.V spesolimab at Week 1 (Wk1)/Day 8 (D8).

Reporting group title	Spesolimab 900 mg i.v. SD
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Reporting group description:

Patients received intravenously (i.v.) a single dose of solution for infusion containing 900 mg of spesolimab on Day 1 (D1) of Week 1 (Wk1). Based on the subsequent treatment response, participants were then to be followed up for 12 to 28 Wk.

If the severity and progression of the disease worsened within the first week the investigator could treat the patient with a Standard of Care (SoC) treatment of his/her choice. If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing SoC since there was an option to administer open label (OL) spesolimab instead at this time. If SoC was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on D8.

If the condition of the patient worsened after Wk1/D8 patients were eligible to receive rescue treatment with open label spesolimab (only one single rescue i.v. dose of 900 mg spesolimab) after Wk1 to Wk 12.

Serious adverse events	Placebo	Rescue Spesolimab 900 mg i.v.	Open Label (OL) D8 Spesolimab 900 mg i.v.
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)	2 / 6 (33.33%)	6 / 27 (22.22%)
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)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 27 (3.70%)
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			
Drug-induced liver injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (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			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (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
Psoriasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pustular psoriasis			
subjects affected / exposed	3 / 18 (16.67%)	2 / 6 (33.33%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	2 / 3	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (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
Infections and infestations			

Influenza			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (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	Spesolimab 900 mg i.v. SD		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 35 (17.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psoriasis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pustular psoriasis			

subjects affected / exposed	4 / 35 (11.43%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Rescue Spesolimab 900 mg i.v.	Open Label (OL) D8 Spesolimab 900 mg i.v.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	4 / 6 (66.67%)	14 / 27 (51.85%)
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1

Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	4 / 18 (22.22%)	2 / 6 (33.33%)	2 / 27 (7.41%)
occurrences (all)	4	3	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypomenorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Eosinophil percentage increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Eosinophil count increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Haematocrit decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
High density lipoprotein decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
High density lipoprotein increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Platelet count increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Protein total decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Tendon injury subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 3 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 1 / 27 (3.70%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Erythropenia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0 0 / 18 (0.00%) 0 0 / 18 (0.00%) 0	1 / 6 (16.67%) 1 1 / 6 (16.67%) 2 1 / 6 (16.67%) 1	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 3 / 27 (11.11%) 3

Nausea subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	0 / 27 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 6 (33.33%) 2	1 / 27 (3.70%) 1
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	2 / 27 (7.41%) 2
Pain of skin subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 6 (0.00%) 0	0 / 27 (0.00%) 0
Psoriasis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	1 / 27 (3.70%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 6 (0.00%) 0	2 / 27 (7.41%) 2
Pustular psoriasis subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 4	2 / 6 (33.33%) 2	5 / 27 (18.52%) 6
Skin erosion subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 6 (16.67%) 1	0 / 27 (0.00%) 0
Urticaria			

subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Joint effusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	1
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	1 / 27 (3.70%)
occurrences (all)	1	1	1
Oligoarthritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	1 / 6 (16.67%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Tendonitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Otitis externa			
subjects affected / exposed	0 / 18 (0.00%)	0 / 6 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Streptococcal infection			

subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pustule			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 6 (16.67%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	1 / 18 (5.56%)	0 / 6 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Spesolimab 900 mg i.v. SD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 35 (65.71%)		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Inflammation			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		

Oedema peripheral subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Pyrexia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Hypomenorrhoea subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
C-reactive protein increased			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	3		
Eosinophil percentage increased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Eosinophil count increased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
High density lipoprotein decreased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
High density lipoprotein increased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Platelet count increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Protein total decreased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Tendon injury			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Syncope subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3		
Erythropenia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Nausea subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4		
Vomiting subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Hepatobiliary disorders			

Hepatic function abnormal subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Erythema subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Pain of skin subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Psoriasis subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Pruritus subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Pustular psoriasis subjects affected / exposed occurrences (all)	17 / 35 (48.57%) 21		
Skin erosion subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Urticaria subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Musculoskeletal and connective tissue disorders			
Joint swelling subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Joint effusion			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Oligoarthritis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Infections and infestations			
Otitis externa			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Streptococcal infection			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Pustule			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2019	<p>Amendment 1 Part 1:</p> <p>Based on Health Authority recommendation, the sample size was increased from 27 to 51 patients (placebo: 17, spesolimab: 34) to enhance the safety database and to allow a more robust assessment of efficacy and of the benefit-risk ratio.</p> <p>Based on Health Authority recommendation, the former 2 co-primary endpoints were changed into a primary and a key secondary endpoint. The statistical design - model, the null and alternative hypotheses, the statistical methods, and the analyses were updated.</p> <p>The methods for the handling of missing data were updated. For the estimand concept for the primary and secondary endpoints at Weeks 1 and 4, death was removed from the items considered as non-response. The wording for the AE collection and reporting was updated. For the Adverse events of special interest (AESI) "hepatic injury", Alanine aminotransferase (ALT) and/or Aspartate aminotransferase (AST) $\geq 10 \times$ Upper limit of normal (ULN) was added to the definition. The AESI "Infusion reactions including anaphylactic reaction" was renamed to "systemic hypersensitivity including infusion reactions" and to the emergency procedures during or after infusion of spesolimab, "Systemic hypersensitivity" was added to the "Infusion reactions including anaphylactic reaction". The definition of disease worsening and scenarios when escape treatment may have been given were clarified.</p> <p>Exclusion criterion #14 regarding active or latent tuberculosis was updated.</p> <p>Former exclusion criterion #16 regarding previous allergy immunotherapy was removed. Risankizumab was added as restricted medication. The washout period was reduced for all biologics to 2 months. The assessment of fever on dosing days was further specified. As tuberculosis test, T-Spot® was also allowed. The eligibility criteria for the open-label extension trial were updated.</p>
19 July 2019	<p>Amendment 1 Part 2:</p> <p>For the biomarker and pharmacogenomic analyses, a staged approach was introduced. Healthcare resource utilization (HCRU) data collection throughout the trial was added. Not flaring within the 6-month screening period was added as screening failure. The requirement to assign a new patient number in the case of re-screening was added.</p>
26 June 2020	<p>The following main changes were introduced by the amendment:</p> <p>To explore the efficacy and safety of open-label spesolimab i.v. treatment on Day 8 was added as additional objective.</p> <p>A set of further endpoints to explore the efficacy of OL spesolimab on Day 8 and information on their analyses were added. 2 further endpoints were added (change from baseline in GPPGA total score by visit, change from baseline in GPPGA pustulation subscore by visit). Time points for a primary analysis at Week 12 (i.e. including data up to Week 12) and a final analysis, if applicable, were added and the blinding plans for these analyses were updated. A sensitivity analysis for the primary endpoint using logistic regression and an estimand for the analysis of secondary continuous endpoints were added. The methods for the handling of missing data were updated.</p> <p>The wording for the AE collection for patients who continued in the extension trial was updated.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A large proportion of patients in both arms had been treated as non-responders at Week 4, and the true efficacy outcomes for the randomized treatment at this time-point were never observed for the analysis.

Notes: