Clinical trial results:
Multicenter, double-blind, placebo-controlled, randomized withdrawal trial with Tadekinig alfa (r-hIL-18BP) in patients with IL-18 driven monogenic autoinflammatory conditions: NLRC4 mutation and XIAP deficiency

Summary

EudraCT number	2018-003297-27
Trial protocol	DE
Global end of trial date	31 October 2023

Results information

Result version number	v1 (current)
This version publication date	17 May 2024
First version publication date	17 May 2024

Trial information

Trial identification

Sponsor protocol code	NLRC4/XIAP.2016.001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03113760
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AB2 Bio Ltd.
Sponsor organisation address	EPFL Innovation Park, Building B, 4th floor, Lausanne, Switzerland, 1015
Public contact	Eduardo Schiffrin, AB2 Bio Ltd., 0041 216940043, eduardo.schiffrin@ab2bio.com
Scientific contact	Eduardo Schiffrin, AB2 Bio Ltd., 0041 216940043, eduardo.schiffrin@ab2bio.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	31 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2023
Global end of trial reached?	Yes
Global end of trial date	31 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess clinical efficacy of Tadekinig alfa in monogenic autoinflammatory diseases with ongoing inflammation and deleterious mutations of NLRC4-MAS or XIAP
- To assess laboratory/biological evidence of efficacy

Protection of trial subjects:

Patient safety and comfort were guiding principles for this clinical trial with Tadekinig alfa. The following measures have been defined in the study protocol:
1. In order to enhance subjects' compliance and avoid subjects' discomfort, local skin treatment were proposed to the parents/patients to mitigate local inflammatory reactions.
2. Collected blood volumes were taking into account the maximum limits for certain age groups.
3. Emergency cards with relevant data on the IMP and clinical trial including the contact data for availability in case of emergencies were provided to the patients.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	21 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	15
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1

Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	6
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment in 11 sites in USA, Canada and Germany

Pre-assignment

Screening details:

A total of 24 patients were screened in the study.
8 patients were screening failures.
1 patient was a screening failure and was re-enrolled upon next disease flare with subsepquent patient number (counted twice for consistency in total number of patients above).

Period 1

Period 1 title	Initial 18 week Treatment - SAOL/RDBPC
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tadekinig alfa SAOL

Arm description:

Including patients treated with Tadekinig alfa from randomized double-blind placebo controlled phase (RDBPC) up to protocol version 3 and from single arm open-label phase (SAOL) from protocol version 4 and subsequent amendments. Both populations had the same treatment schedule and are analysed together in the final analysis.

Arm type	Experimental
Investigational medicinal product name	Tadekinig alfa
Investigational medicinal product code	
Other name	r-hIL-18BP
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 mg/kg s.c. every 2 days ± 5 hours

Arm title	Placebo RDBPC

Arm description:

Including patients from randomized double-blind placebo controlled phase (RDBPC) up to protocol version 3 randomized to placebo treatment.

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

Dosage and administration details:

Equivalent volume of Placebo s.c. every 2 days ± 5 hours

Number of subjects in period 1	Tadekinig alfa SAOL	Placebo RDBPC
Started	14	1
Completed	10	0
Not completed	4	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-
Disease relapse	1	1

Period 2

Period 2 title	Randomized Withdrawal Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Tadekinig alfa

Arm description:

Active treatment arm in Randomized Withdrawal Phase

Arm type	Experimental
Investigational medicinal product name	Tadekinig alfa
Investigational medicinal product code	
Other name	r-hIL-18BP
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 mg/kg s.c. every 2 days ± 5 hours

Arm title	Placebo

Arm description:

Placebo treatment arm in Randomized Withdrawal Phase

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

Dosage and administration details:

Equivalent volume of Placebo s.c. every 2 days ± 5 hours

Number of subjects in period 2	Tadekinig alfa	Placebo
Started	5	5
Completed	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Initial 18 week Treatment - SAOL/RDBPC
Reporting group description:	
Patients receiving active treatment with Tadekinig alfa (14) or Placebo (1) during the first 18 weeks	

Reporting group values	Initial 18 week Treatment - SAOL/RDBPC	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	1	1	
Infants and toddlers (28 days-23 months)	4	4	
Children (2-11 years)	6	6	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	4	4	
Male	11	11	

End points

End points reporting groups

Reporting group title	Tadekinig alfa SAOL
Reporting group description:	
Including patients treated with Tadekinig alfa from randomized double-blind placebo controlled phase (RDBPC) up to protocol version 3 and from single arm open-label phase (SAOL) from protocol version 4 and subsequent amendments. Both populations had the same treatment schedule and are analysed together in the final analysis.	
Reporting group title	Placebo RDBPC
Reporting group description:	
Including patients from randomized double-blind placebo controlled phase (RDBPC) up to protocol version 3 randomized to placebo treatment.	
Reporting group title	Tadekinig alfa
Reporting group description:	
Active treatment arm in Randomized Withdrawal Phase	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment arm in Randomized Withdrawal Phase	

Primary: Time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase

End point title	Time to first occurrence of disease reactivation (including full and partial disease reactivation) during the RW phase
End point description:	
Median time to first occurrence of DR was 2.71 weeks for the placebo group, and was not applicable in the TA group due to the small number of patients (2 patients) with a disease reactivation. Therefore, 25th Percentile was entered below for results. Time to 80% event free was 1.93 weeks for placebo and 7.57 weeks for Tadekinig alfa.	
End point type	Primary
End point timeframe:	
Time to First Occurrence of Disease Reactivation during the RW Phase (up to 16 weeks)	

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Weeks				
median (confidence interval 95%)	11.43 (4.0 to 11.43)	2.29 (1.86 to 2.71)		

Attachments (see zip file)	2018-003297-27_Primary Endpoint KaplanMeier/2018-003297-

Statistical analyses

Statistical analysis title	Primary per protocol analysis

Statistical analysis description:

Primary analysis adhering to per protocol criteria.

Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1492
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	2.11

Notes:

[1] - Tadekinig alfa is compared to placebo using the log rank test. Kaplan-Meier (KM) estimates of the distribution of time-to-event are summarized and graphed by treatment group. Greenwood's formula is used to estimate the standard error of the KM statistic. The primary analysis endpoint is tested at a 2-sided alpha level of 0.05.

Statistical analysis title	Sensitivity analysis for patient 14-001 (no DR)[2]

Statistical analysis description:

Patient 14-001 was patient with XIAP-deficiency and frequent flares (>60) requiring increased corticosteroids prior to enrolment. Disease reactivation criteria in RW phase were met by transient abdominal symptoms of pain/colic & diarrhea and CRP exactly twice upper limit of normal; no additional usual disease manifestations observed. Disease reactivation was self-resolving without steroids, as opposed to prior flares. Sensitivity analysis reasseses this patient as not flaring in RW phase.

Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0494
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0

Notes:

[2] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: The upper limit is reported as not applicable and therefore left empty.

Secondary: Response to therapy (including complete response and partial response) in the SAOL phase from Week 10 onwards and observed at least at 2 consecutive visits at least 2 weeks apart during the SAOL phase

End point title	Response to therapy (including complete response and partial response) in the SAOL phase from Week 10 onwards and observed at least at 2 consecutive visits at least 2 weeks apart during the SAOL phase[3]

End point description:

Key secondary efficacy endpoint; patients who discontinued prior to Week 10 are non-responders.

End point type	Secondary

End point timeframe:

18 week initial treatment phase for patients with active treatment with Tadekinig alfa

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Response to Therapy During the SAOL Phase

End point title	Best Response to Therapy During the SAOL Phase[4]

End point description:

Complete response
- No major end organ damage (=objective mAIDAI components)
- No systemic inflammation
- Discontinuation of immunosuppressive therapy (systemic steroids or other)

Partial Response
- Resolution of at least 50% of major end organ damage
- and 50% of markers normalized or discontinuation of immunosuppressive therapy (systemic steroids or other)

Disease improvement
- Resolution of at least 1 major end-organ or normalization or 50% decrease of marker
- No dose increase of immunosuppressive therapies

End point type	Secondary

End point timeframe:

18 week initial treatment phase with Tadekinig alfa

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
Complete response	1			
Partial response	10			
Disease improvement	3			
No improvement	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response to Therapy during the SAOL Phase

End point title	Duration of Response to Therapy during the SAOL Phase[5]

End point description:

Duration of response to therapy is only assessed for patients with a complete or partial response to therapy during SAOL as defined in the statistical analysis plan and is defined as the time from first assessment indicating partial or complete response until the time of subsequent disease reactivation.
The median duration of response to therapy during the SAOL Phase was not estimable, due to the small percentage of patients who experienced a disease reactivation.
Minimum duration of response was 2.1 weeks; maximum duration of response was 19.0 weeks.

End point type	Secondary

End point timeframe:

18 weeks in the initial treatment phase with Tadekinig alfa

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Weeks				
median (confidence interval 95%)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Reactivation Rate per Week during the SAOL Phase

End point title	Disease Reactivation Rate per Week during the SAOL Phase[6]

End point description:

Number of disease reactivations for treated patients
The mean disease reactivation rate per week was 0.0 (with SD 0.09) and min/max of 0.0/0.3.

End point type	Secondary

End point timeframe:

18 weeks initial treatment phase with Tadekinig alfa

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Disease reactivations				
0 Disease Reactivations	11			
1 Disease Reactivations	1			
2 Disease Reactivations	2			
3 Disease Reactivations	0			
>3 Disease Reactivations	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment failures (i.e. patients who experience at least one disease reactivation) during the SAOL phase

End point title	Treatment failures (i.e. patients who experience at least one disease reactivation) during the SAOL phase[7]

End point description:

Treatment failures were defined as patients who experienced at least 1 disease reactivation. Disease reactivation includes full or partial disease reactivation after the first assessment indicating partial or complete response during the SAOL phase as defined in the statistical analysis plan.

End point type	Secondary

End point timeframe:

18 week initial treatment phase with Tadekinig alfa

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Ferritin during the SAOL Phase by Visit

End point title	Change from Baseline in Serum Ferritin during the SAOL Phase by Visit[8]

End point description:

End point type	Secondary

End point timeframe:

18 week initial treatment phase with tadekinig alfa

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Serum Ferritin (ng/mL)				
arithmetic mean (standard deviation)				
Change from Baseline to Week 1	-3333.1 (± 7008)			
Change from Baseline to Week 2	-6061.1 (± 13168.11)			
Change from Baseline to Week 3	-5488.0 (± 12882.6)			
Change from Baseline to Week 4	-1970.6 (± 8216.18)			
Change from Baseline to Week 8	-5761.1 (± 10439.98)			
Change from Baseline to Week 12	-7032.6 (± 14345.88)			
Change from Baseline to Week 18	-8558.7 (± 15700.51)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CRP during the SAOL Phase by Visit

End point title	Change from Baseline in CRP during the SAOL Phase by Visit[9]

End point description:

End point type	Secondary

End point timeframe:

18 weeks initial treatment pahse with Tadekinig alfa

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: CRP (mg/dL)				
arithmetic mean (standard deviation)				
Change from Baseline to Week 1	-2.35 (± 3.364)			
Change from Baseline to Week 2	-1.46 (± 5.736)			
Change from Baseline to Week 3	-2.53 (± 4.339)			
Change from Baseline to Week 4	-2.26 (± 3.813)			
Change from Baseline to Week 8	-2.04 (± 4.817)			
Change from Baseline to Week 12	-2.21 (± 4.730)			
Change from Baseline to Week 18	-2.28 (± 4.279)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of Disease Reactivations: Change from Baseline in mAIDAI Total Score in the SAOL phase

End point title	Intensity of Disease Reactivations: Change from Baseline in mAIDAI Total Score in the SAOL phase[10]

End point description:

The mAIDAI (modified autoinflammatory disease activitiy index) is an assessment of global disease activity that measures 14 different components for disease as either absent (0 points) or present (2 points for Uveitis 3+/4+ and 1 point for all other
symptoms) at each visit. The mAIDAI total score is the sum of the points assigned across all components and ranges from 0 to 15, with a higher score indicating more severe disease activity.

End point type	Secondary

End point timeframe:

18 week initial treatment phase with Tadekinig alfa

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: mAIDAI				
arithmetic mean (standard deviation)				
Change from Baseline to Week 1	-2.0 (± 1.62)			
Change from Baseline to Week 2	-2.6 (± 1.45)			
Change from Baseline to Week 3	-2.6 (± 1.28)			
Change from Baseline to Week 4	-2.5 (± 1.22)			
Change from Baseline to Week 8	-3.1 (± 1.73)			
Change from Baseline to Week 12	-3.5 (± 1.37)			
Change from Baseline to Week 18	-3.9 (± 0.74)			

Attachments (see zip file)	2018-003297-27_Secondary Endpoint mAIDAI in SAOL/2018-

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PGA Symptom Severity Score during the SAOL Phase

End point title	Change from Baseline in PGA Symptom Severity Score during the SAOL Phase[11]

End point description:

The PGA (Physician Global Assessment) assesses the severity of disease-related (auto-inflammatory) symptoms by selecting an integer score from 0 (no symptoms) to 10 (highest severity of symptoms possible).

End point type	Secondary

End point timeframe:

18 week initial treatment phase with Tadekinig alfa

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Physician Global Assessment				
arithmetic mean (standard deviation)				
Change from Baseline to Week 1	-2.8 (± 2.19)			
Change from Baseline to Week 2	-3.7 (± 2.43)			
Change from Baseline to Week 3	-4.0 (± 2.11)			
Change from Baseline to Week 4	-3.2 (± 2.52)			
Change from Baseline to Week 8	-4.8 (± 2.42)			
Change from Baseline to Week 12	-5.1 (± 2.39)			

Change from Baseline to Week 18	-5.8 (± 2.10)			

Attachments (see zip file)	2018-003297-27_Secondary Endpoint PGA in SAOL/2018-

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of individual disease components during SAOL phase, if present at Baseline

End point title	Resolution of individual disease components during SAOL phase, if present at Baseline[12]

End point description:

Resolution of Individual mAIDAI Components during the SAOL phase from Baseline to Week 18/early termination.
Number displays percentage of patients with resolution of individual disease component at Week 18 or early termination visit based on the number of patients with a baseline assessment for the component of interest.

End point type	Secondary

End point timeframe:

18 weeks initial treatment phase with Tadekinig alfa

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
Fever	100			
Abdominal Pain/Colic	80			
Nausea/Vomiting	87			
Diarrhea	77			
Transaminitis	30			
Organomegaly	54			
Rash	75			
Uveitis	100			
Arthralgia	100			
Arthritis	0			
Cytopenia	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Patient/Caregiver Qualitative Evaluation of Health Status in SAOL phase

End point title	Change in Patient/Caregiver Qualitative Evaluation of Health Status in SAOL phase[13]

End point description:

The Sum of individual disease-related symptoms score is the sum of (x) individual symptom scores within domain each ranging from 0 (None) to 5 (Very severe): general wellbeing (5), gastrointestinal (7), musculoskeletal (5), skin (2), eye (2), central nervous system (3), and lymphatic (2). Patient/Caregiver Qualitative Evaluation of Health Status was implemented in protocol version 6; thus only completed by 5 patients.

End point type	Secondary

End point timeframe:

18 weeks initial treatment phase with Tadekinig alfa

Notes:

[13] - 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 endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Individual disease-related symptom score				
arithmetic mean (standard deviation)				
Mean at Baseline	40.5 (± 7.78)			
Mean at Week 18	7.6 (± 8.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalizations during the SAOL Phase

End point title	Hospitalizations during the SAOL Phase[14]

End point description:

Hospitalization at SAOL Baseline was any hospitalization prior to the first dose of study drug during the SAOL Phase. Subsequent Hospitalizations during SAOL Phase included any additional hospitalization after study drug administation.

End point type	Secondary

End point timeframe:

18 week initial treatment with with Tadekinig alfa

Notes:

[14] - 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 endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started

with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Patients				
Patients not Hospitalized at SAOL Baseline	6			
Patients Hospitalized at SAOL Baseline	8			
No Subsequent Hospitalizations during SAOL	10			
1 Subsequent Hospitalization during SAOL	1			
2 Subsequent Hospitalizations during SAOL	2			
3 or more Subsequent Hospitalizations during SAOL	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 34/ET in Serum Ferritin During the RW Phase

End point title	Change from Baseline to Week 34/ET in Serum Ferritin During the RW Phase

End point description:

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Serum Ferritin (ng/mL)				
arithmetic mean (standard deviation)	-109.5 (± 167.40)	211.8 (± 359.10)		

Statistical analyses

Statistical analysis title	Mann-Whitney-Wilcoxon test

Statistical analysis description:

P-values comparing change from RW Baseline among treatment groups were rank-based using the Mann-Whitney-Wilcoxon test

Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0317
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline to Week 34/ET in CRP During the RW Phase

End point title	Change from Baseline to Week 34/ET in CRP During the RW Phase

End point description:

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: CRP (mg/dL)				
arithmetic mean (standard deviation)	-0.02 (± 0.199)	0.24 (± 1.354)		

Statistical analyses

Statistical analysis title	Mann-Whitney- Wilcoxon
Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4603
Method	Wilcoxon (Mann-Whitney)

Secondary: Intensity of Disease Reactivations: Change from Baseline in mAIDAI Total Score in RW Phase

End point title	Intensity of Disease Reactivations: Change from Baseline in mAIDAI Total Score in RW Phase

End point description:

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: mAIDAI Total Score				
median (standard deviation)	-0.4 (± 0.89)	1.0 (± 1.73)		

Statistical analyses

Statistical analysis title	Mann-Whitney- Wilcoxon
Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from Baseline to Week 34/ET in PGA During the RW Phase

End point title	Change from Baseline to Week 34/ET in PGA During the RW Phase

End point description:

The PGA (Physician Global Assessment) assesses the severity of disease-related (auto-inflammatory) symptoms by selecting an integer score from 0 (no symptoms) to 10 (highest severity of symptoms possible).

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Physician Global Assessment				
arithmetic mean (standard deviation)	0.4 (± 0.89)	2.0 (± 3.39)		

Statistical analyses

Statistical analysis title	Mann-Whitney- Wilcoxon
Comparison groups	Tadekinig alfa v Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7619
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in Patient/Caregiver Qualitative Evaluation of Health Status in RW Phase

End point title	Change in Patient/Caregiver Qualitative Evaluation of Health Status in RW Phase

End point description:

Change from Baseline to Week 34/ET in Sum of individual disease-related symptoms During the RW Phase
The individual disease-related symptoms scores were the sum of (x) individual symptom scores within domain each ranging from 0 (None) to 5 (Very severe): general wellbeing (5), gastrointestinal (7), musculoskeletal (5), skin (2), eye (2), central nervous system (3), and lymphatic (2).

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Individual disease-related symptom score				
arithmetic mean (standard deviation)				
Mean at Week 18 (start of RW phase)	11.3 (± 8.62)	2.0 (± 2.83)		
Mean at Week 34 or Early Termination	7.7 (± 7.09)	46.0 (± 14.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalizations during the RW Phase

End point title	Hospitalizations during the RW Phase

End point description:

End point type	Secondary

End point timeframe:

Up to 16 weeks randomized withdrawal phase; change from Week 18 to Week 34 or Early termination visit

End point values	Tadekinig alfa	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Number of Hospitalizations	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Hospitalization in SAOL phase

End point title	Length of Hospitalization in SAOL phase[15]

End point description:

No hospitalizations occured during the randomized withdrawal phase; thus endpoint only listed for SAOL phase.

End point type	Secondary

End point timeframe:

18 weeks initial treatment phase with Tadekinig alfa

Notes:

[15] - 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 endpoint assesses all patients with active treatment in the initial 18 weeks treatment phase (SAOL = single arm open label phase). One patient enrolled in the early protocol version 3 started with placebo in the first treatment phase and is therefore excluded from the endpoint analysis for the SAOL phase.

End point values	Tadekinig alfa SAOL			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Days				
arithmetic mean (standard deviation)				
Length of Baseline Hospitalization	44.8 (± 25.57)			
Length of Subsequent Hospitalizations in SAOL	18.0 (± 26.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored and recorded from the time the informed consent is signed until completion of the study (Visit 13) or premature withdrawal.

Adverse event reporting additional description:

Day to day fluctuations of the underlying disease of interest or other pre-existing disease or conditions present or detected at the start of the study were not to be reported as separate adverse events but assessed via the modified autoinflammatory disease index (mAIDAI) at scheduled or unscheduled visits in case of a disease reactivation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Initial 18 week Tadekinig alfa Treatment

Reporting group description:

All patients starting with active treatment during the initial 18 weeks treatment phase - Single arm open label full analysis set (SAOL-FAS)

Reporting group title	Initial 18 week Placebo Treatment

Reporting group description:

Patients received placebo in first treatment phase under protocol version 3

Reporting group title	Randomized Withdrawal Phase - Active

Reporting group description:

Patients receiving Tadekinig alfa during Randomized Withdrawal Phase

Reporting group title	Randomized Withdrawal Phase - Placebo

Reporting group description:

Patients receiving Placebo during Randomized Withdrawal Phase

Reporting group title	Screening phase

Reporting group description:

Adverse events reported prior to first dose of Tadekinig alfa or placebo.

Serious adverse events	Initial 18 week Tadekinig alfa Treatment	Initial 18 week Placebo Treatment	Randomized Withdrawal Phase - Active
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)	0 / 1 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (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	Randomized Withdrawal Phase - Placebo	Screening phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Initial 18 week Tadekinig alfa Treatment	Initial 18 week Placebo Treatment	Randomized Withdrawal Phase - Active
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	1 / 1 (100.00%)	4 / 5 (80.00%)
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	5 / 14 (35.71%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	41	0	9
Injection site erythema			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	10	0	1
Injection site pain			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	15	0	5
Pyrexia			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	10	0	1
Asthenia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Condition aggravated			

subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Injection site swelling			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	4	0	1
Hypothermia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Injection site reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Complication associated with device			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Secretion discharge			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Atelectasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Epistaxis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pulmonary hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Investigations			
C-reactive protein increased			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	2 / 5 (40.00%)
occurrences (all)	6	0	2
Red blood cell sedimentation rate increased			
subjects affected / exposed	3 / 14 (21.43%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Alanine aminotransferase increased			

subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 14 (14.29%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Adenovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Coronavirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Human rhinovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Interleukin-2 receptor increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Sapovirus test positive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Serum ferritin increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Transaminases increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Weight decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vital signs measurement			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	5
Overdose			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Transfusion reaction			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Wrist fracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Coronary artery dilatation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Fontanelle bulging			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Somnolence			

subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Splenomegaly			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Ocular hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 14 (35.71%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	7	1	0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Inflammatory bowel disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lower gastrointestinal haemorrhage			

subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	5	0	1
Abdominal pain			
subjects affected / exposed	3 / 14 (21.43%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	6	1	0
Abdominal distension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Poisoning	Additional description: Food poisoning		
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Teething			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hepatobiliary disorders			

Hepatosplenomegaly			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 14 (28.57%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	10	0	0
Acne			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Ingrowing nail			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Macule			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Palmar erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 14 (21.43%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Pain in extremity			
subjects affected / exposed	3 / 14 (21.43%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Groin pain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Joint effusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Synovitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Coronavirus infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Epstein-Barr viraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tinea infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Localised infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
External ear cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Groin abscess			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Furuncle			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Subcutaneous abscess			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Decreased appetite			

subjects affected / exposed	0 / 14 (0.00%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fluid retention			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hepatic steatosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 1 (100.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 1 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Randomized Withdrawal Phase - Placebo	Screening phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	7 / 15 (46.67%)	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Pyrexia			

subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Asthenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Condition aggravated			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Injection site swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hypothermia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Injection site reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Complication associated with device			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Secretion discharge			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Atelectasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Pulmonary hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Rales			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Investigations			
C-reactive protein increased			

subjects affected / exposed	0 / 5 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Red blood cell sedimentation rate increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Adenovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
Coronavirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Cytomegalovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Interleukin-2 receptor increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Sapovirus test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Serum ferritin increased			

subjects affected / exposed	0 / 5 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Transaminases increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Vital signs measurement			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Overdose			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Transfusion reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Wrist fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Coronary artery dilatation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Fontanelle bulging			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Splenomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Colitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Poisoning	Additional description: Food poisoning		
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Frequent bowel movements			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Teething			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Dental caries			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hepatosplenomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	8	0	
Acne			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Ingrowing nail			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Macule			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Palmar erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Joint effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Limb discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Osteonecrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Osteoporosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Synovitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Coronavirus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Epstein-Barr viraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

Otitis media				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Tinea infection				
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
Localised infection				
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
External ear cellulitis				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Groin abscess				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Furuncle				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Hordeolum				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Respiratory tract infection				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Upper respiratory tract infection				
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
Subcutaneous abscess				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Urinary tract infection				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		

Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hepatic steatosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2017	Protocol verison 2.0 - This first protocol amendment, resulting in Protocol version 2.0 dated 21 Feb 2017, implements some changes following FDA recommendations (Study May Proceed cover letter ref ID 4035810, dated January 3, 2017). Some suggestions as discussed during the investigator meeting were considered to allow better understanding and to further clarify the study requirements.
07 April 2017	Protocol version 3.0 - With reference to FDA correspondence dated 15 March 2017, this second protocol amendment (Protocol version 3.0 dated 07 April 2017) implements FDA' recommendation to incorporate a Randomized Withdrawal Phase after the first 18-week treatment phase (Randomized Double-Blind Placebo-Control phase) as an additional assessment of efficacy.
02 October 2018	Protocol version 4.0 - Recruitment rates for this rare genetic condition were lower than expected and after discussion with investigators the main reason for the low recruitment was the initial placebo-controlled part of the study which raises ethical concerns. Thus, the initial placebo arm of the study during the first 18-weeks treatment phase was changed to a single arm open label (SAOL) design. The subsequent 8 week randomized double blind placebo control phase remained as assessment of primary efficacy.
17 May 2019	Protocol version 4.1 - Minor changes in protocol in response to regulatory authority review (e.g. addition of exclusion criterion for patient with hypersensitivity towards active substance or excipients; clarification for use of permitted and prohibited conconmitant medications; addition of creatinine and glomerular filtration rate to safety laboratory parameters measured)
29 January 2021	Protocol version 5 - Following a significant delay in recruitment during the COVID-19 pandemic and following a meeting with the FDA on 17 Dec 2020, this protocol amendment (Protocol version 5.0 dated 29 Jan 2021) allows the inclusion of adult patients with NLRC4 mutation and XIAP deficiency, for which the monogenic autoinflammatory condition is not well controlled. It also specifies that patients with XIAP deficiency and an unsuccessful previous bone marrow transplantation are allowed for inclusion. Furthermore, the duration of the double-blind placebo-controlled randomized withdrawal (RW) phase is prolonged from 8 weeks to a maximum of 16 weeks with a premature stop of blinded treatment in case of a disease flare.
03 September 2021	Protocol version 6 - Following a clinical outcome assessment focused type C meeting with the FDA on 23 Jun 2021 and a scientific advice discussion meeting with the EMA on 31 Aug 2021, this protocol amendment (Protocol version 6.0 dated 03 Sep 2021) implements changes to the assessment of response to therapy and disease reactivation. The implemented changes reflect the newly gained knowledge about the disease since the initial study design and take into consideration the individual disease severity of each patient and heterogeneity of the disease. Furthermore, a questionnaire exploring the patient’s or caregiver’s evaluation of the health status at baseline and at the end of each treatment phase was implemented for all patients treated under this protocol version. Finally, the selection criteria were slightly revised to lower the hurdles for enrolment for patients in a severe disease status requiring immediate start of study drug treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported