



## Clinical trial results:

### A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Immune-Mediated Necrotizing Myopathy

#### Summary

EudraCT number	2019-001497-29
Trial protocol	FR NL
Global end of trial date	14 June 2021

#### Results information

Result version number	v2 (current)
This version publication date	03 June 2022
First version publication date	19 March 2022
Version creation reason	

#### Trial information

##### Trial identification

Sponsor protocol code	RA101495-02.202
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04025632
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	UCB Biosciences GmbH
Sponsor organisation address	Alfred-Nobel-Strasse 10, Monheim, Germany, 40789
Public contact	Clin Trial Reg & Results Disclosure, UCB Biosciences GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB Biosciences GmbH, clinicaltrials@ucb.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	02 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2021
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of zilucoplan over placebo in creatine kinase (CK) levels in study participants with immune-mediated necrotizing myopathy (IMNM).

Protection of trial subjects:

This study was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

Background therapy:

All standard of care therapy medications for IMNM were kept at the same doses throughout the study, including corticosteroids, immunosuppressive drugs, and intravenous immunoglobulin (IVIG).

Evidence for comparator: -

Actual start date of recruitment	07 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	27
EEA total number of subjects	5

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)	21
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was performed in 4 countries (France, the Netherlands, the United Kingdom, and the United States of America) between 07 November 2019 and 14 June 2021.

### Pre-assignment

Screening details:

Of the 37 participants who were screened, 27 participants with IMNM were randomized in a 1:1 ratio to receive zilucoplan 0.3 mg/kg or a matching placebo for the 8-week Treatment Period in the Main Portion. All eligible participants were given the option to receive daily subcutaneous (SC) zilucoplan 0.3 mg/kg in the Extension Portion.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Participants were randomized to receive daily SC doses of matching placebo during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.

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:

Daily SC injection over the 8-week study period.

<b>Arm title</b>	Zilucoplan 0.3 mg/kg
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Arm description:

Participants were randomized to receive daily SC doses of zilucoplan 0.3 mg/kg during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.

Arm type	Experimental
Investigational medicinal product name	Zilucoplan
Investigational medicinal product code	RA101495
Other name	ZLP
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Daily SC injection over the 8-week study period.

<b>Number of subjects in period 1</b>	Placebo	Zilucoplan 0.3 mg/kg
Started	15	12
Completed Main Portion	15	12
Started Main Portion Safety Follow-up	2	0
Completed Main Portion Safety Follow-up	0	0
Started Extension Portion	13	12
Completed	0	0
Not completed	15	12
Consent withdrawn by subject	1	1
Physician decision	3	1
Adverse event, non-fatal	1	1
Study terminated by sponsor	10	9

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were randomized to receive daily SC doses of matching placebo during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.	
Reporting group title	Zilucoplan 0.3 mg/kg
Reporting group description:	
Participants were randomized to receive daily SC doses of zilucoplan 0.3 mg/kg during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.	

Reporting group values	Placebo	Zilucoplan 0.3 mg/kg	Total
Number of subjects	15	12	27
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.8	56.9	
standard deviation	± 13.6	± 9.0	-
Gender categorical Units: Subjects			
Female	7	6	13
Male	8	6	14
Ethnicity Units: Subjects			
Hispanic or Latino	4	5	9
Not Hispanic or Latino	8	5	13
Unknown or Not Reported	3	2	5
Race Units: Subjects			
American Indian/ Alaska native	0	0	0
Asian	0	0	0
Black or African American	1	3	4
Native Hawaiian or other Pacific Islander	0	0	0
White	10	7	17
Other/Mixed	0	0	0
Unknown or Not Reported	1	0	1
Missing	3	2	5

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants were randomized to receive daily SC doses of matching placebo during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.	
Reporting group title	Zilucoplan 0.3 mg/kg
Reporting group description: Participants were randomized to receive daily SC doses of zilucoplan 0.3 mg/kg during the 8-week Main Portion of the study. All eligible participants were given the option to receive daily SC zilucoplan 0.3 mg/kg in the Extension Portion of the study.	
Subject analysis set title	Main Portion: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were randomized to receive daily SC doses of matching placebo during the 8-week Main Portion of the study.	
Subject analysis set title	Main Portion: Zilucoplan 0.3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants were randomized to receive daily SC doses of zilucoplan 0.3 mg/kg during the 8-week Main Portion of the study.	
Subject analysis set title	Extension Portion: Zilucoplan 0.3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received daily SC doses of zilucoplan 0.3 mg/kg during the Extension Portion of the study.	

### Primary: Percentage Change From Baseline to Week 8 in Serum CK Levels

End point title	Percentage Change From Baseline to Week 8 in Serum CK Levels
End point description: All laboratory samples were obtained prior to administration of study drug at applicable visits. CK levels were measured by a central laboratory. The Intent-to-Treat (ITT) Population included all randomized study participants. The ITT population with no missing observations at Baseline and Week 8.	
End point type	Primary
End point timeframe: Baseline (Day 1) and end of Main Portion (Week 8)	

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: percentage change				
arithmetic mean (standard deviation)	-20.72 (± 31.22)	-9.86 (± 26.06)		

### Statistical analyses

<b>Statistical analysis title</b>	Placebo versus (vs) Zilucoplan 0.3 mg/kg
Statistical analysis description:	
The p-value was calculated using a 2-sided Van Elteren test, which represents an extension of the Wilcoxon rank sum test for comparing 2 treatments in a stratified experiment using within-stratum ranks assigning greater weight to rank sums from smaller strata. The magnitude of association between treatment groups was expressed as in Wilcoxon-Mann-Whitney odds followed by the 95% confidence intervals.	
Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.464
Method	2-sided Van Elteren test
Parameter estimate	Wilcoxon-Mann-Whitney odds
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.57

### Primary: Number of Participants Who Experienced a Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced a Treatment-Emergent Adverse Event (TEAE) <sup>[1]</sup>
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End point description:

A TEAE was defined as:

- An adverse event (AE) that occurred after study treatment start that was not present at the time of treatment start.
- An AE that increased in severity after treatment start if the event was present at the time of treatment start.

The Safety Population included all participants who have received at least 1 dose of study drug, with participants analyzed based on the actual study treatment received.

End point type	Primary
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End point timeframe:

Baseline (Day 1) to end of Main Portion (Week 8)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No additional statistical analysis was pre-specified for this end point.

<b>End point values</b>	Main Portion: Placebo	Main Portion: Zilucoplan 0.3 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	12		
Units: participants	13	9		

### Statistical analyses



## Secondary: Number of Participants Who Achieve at Least Minimal Response Based on the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) Response Criteria Scale

End point title	Number of Participants Who Achieve at Least Minimal Response Based on the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) Response Criteria Scale
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### End point description:

The ACR/EULAR scale utilized a conjoint analysis-based continuous model using absolute percent change from Baseline in core set measures (physician, patient, and Myositis Disease Activity Assessment Tool (MDAAT); muscle strength; Health Assessment Questionnaire (HAQ); and muscle enzyme levels). A total improvement score (range 0-100) was determined by summing scores for each core set measure and comparing improvement in each respective core set measure. The threshold for minimal improvement was  $\geq 20$  in the total improvement score with higher scores indicating a better outcome. The ITT Population with no missing observations at Baseline and Week 8.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) and end of Main Portion (Week 8)	

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	11		
Units: participants	7	6		

## Statistical analyses

Statistical analysis title	Placebo vs Zilucoplan 0.3 mg/kg
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### Statistical analysis description:

The p-value for the comparison of treatment groups was calculated using logistic regression with investigational medicinal product and strata as fixed factors.

Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	5.535

## Secondary: Change From Baseline to Week 8 in Triple Timed Up and Go Test (3TUG) Time

End point title	Change From Baseline to Week 8 in Triple Timed Up and Go Test (3TUG) Time
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### End point description:

The 3TUG test involved the ambulatory participant getting up from a seated position in a chair, walking at their normal pace for 3 meters, turning around, walking back to the chair, and sitting down. This sequence was repeated 3 times without rest, and the 3TUG test time is the average of the 3 lap times. A negative change from baseline indicated a better outcome. The ITT Population with no missing observations at Baseline and Week 8. The test was also only performed in participants who were ambulatory.

End point type	Secondary
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### End point timeframe:

Baseline (Day 1) and end of Main Portion (Week 8)

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: seconds				
least squares mean (standard error)	-0.712 ( $\pm$ 0.789)	-1.401 ( $\pm$ 0.788)		

## Statistical analyses

Statistical analysis title	Placebo vs Zilucoplan 0.3 mg/kg
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### Statistical analysis description:

The p-value was based on a linear model with treatment and strata (anti-3-hydroxy-3-methyl-glutarylcoenzyme A reductase [HMGCR]+/anti-signal recognition particle [SRP]+) as fixed factors with Baseline 3TUG as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.

Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	Linear Mixed Effect Model
Parameter estimate	Least squares (LS) mean difference
Point estimate	-0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.781
upper limit	1.404

## Secondary: Change From Baseline to Week 8 in Proximal Manual Muscle Testing (MMT) Score

End point title	Change From Baseline to Week 8 in Proximal Manual Muscle Testing (MMT) Score
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End point description:

The proximal MMT assessed muscle strength using manual muscle testing in 7 muscle groups (left and right sides assessed separately). The total MMT score for this study, inclusive of both sides, could range from 0-140, where 0 means no strength in any muscles and 140 means full strength in all the muscles examined. A negative change from Baseline indicated a worse outcome. The ITT Population with no missing observations at Baseline and Week 8.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and end of Main Portion (Week 8)

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	11		
Units: score on a scale				
least squares mean (standard error)	-0.18 (± 3.44)	3.71 (± 3.81)		

## Statistical analyses

Statistical analysis title	Placebo vs Zilucoplan 0.3 mg/kg
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Statistical analysis description:

The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline proximal MMT as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.

Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.431
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.18
upper limit	13.95

## Secondary: Change From Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS) Score

End point title	Change From Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS) Score
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End point description:

The Physician Global Activity VAS Score measured the treating physician's global evaluation of the participant's overall disease activity using a 10 cm VAS labelled with "no activity" at the left end and "maximum activity" at the right end. The Physician Global Activity VAS Score ranged from 0 (absent extramuscular disease activity) to 10 (maximum extramuscular disease activity). A negative change from Baseline indicated a better outcome. The ITT Population with no missing observations at Baseline and Week 8.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and end of Main Portion (Week 8)

<b>End point values</b>	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: score on a scale				
least squares mean (standard error)	-0.626 ( $\pm$ 0.557)	-0.830 ( $\pm$ 0.671)		

## Statistical analyses

<b>Statistical analysis title</b>	Placebo vs Zilucoplan 0.3 mg/kg
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Statistical analysis description:

The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline Physician Global Activity VAS as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.

Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	-0.204
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.855
upper limit	1.448

## Secondary: Change From Baseline to Week 8 in Patient Global Activity VAS Score

End point title	Change From Baseline to Week 8 in Patient Global Activity VAS
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	Score
End point description:	
The Patient Global Activity VAS Score measured the treating participant's global evaluation of their overall disease activity using a 10 cm VAS labelled with "no activity" at the left end and "maximum activity" at the right end. The Patient Global Activity VAS score ranged from 0 (absent extramuscular disease activity) to 10 (maximum extramuscular disease activity). A negative change from Baseline indicated a better outcome. The ITT Population with no missing observations at Baseline and Week 8.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) and end of Main Portion (Week 8)	

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: score on a scale				
least squares mean (standard error)	-0.685 ( $\pm$ 0.707)	-1.966 ( $\pm$ 0.854)		

## Statistical analyses

Statistical analysis title	Placebo vs Zilucoplan 0.3 mg/kg
Statistical analysis description:	
The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline Patient Global Activity VAS as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.	
Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.221
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	-1.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	0.829

## Secondary: Change From Baseline to Week 8 in HAQ Score

End point title	Change From Baseline to Week 8 in HAQ Score
End point description:	
The HAQ had 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities with 2 to 3 questions for each section. Scoring within each section ranged from 0 (without any difficulty) to 3 (unable to do). The total HAQ score was then calculated by summing the scores and dividing by the number of categories answered. The total HAQ score for this study could range from 0-3, where 0	

means no functional impairment and 3 means complete functional impairment. A negative change from Baseline indicated a better outcome. The ITT Population with no missing observations at Baseline and Week 8.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) and end of Main Portion (Week 8)	

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: score of a scale				
least squares mean (standard error)	0.022 ( $\pm$ 0.151)	-0.125 ( $\pm$ 0.183)		

## Statistical analyses

<b>Statistical analysis title</b>	Placebo vs Zilucoplan 0.3 mg/kg
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Statistical analysis description:

The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline HAQ as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.

Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.508
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	-0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.601
upper limit	0.307

## Secondary: Change From Baseline to Week 8 in MDAAT Extramuscular Disease Activity VAS Score

End point title	Change From Baseline to Week 8 in MDAAT Extramuscular Disease Activity VAS Score
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End point description:

The MDAAT extramuscular disease activity VAS score measured the degree of disease activity of extramuscular organ systems and muscle. The scoring was performed by the physician and ranged from 0 (absent extramuscular disease activity) to 10 (maximum extramuscular disease activity). A negative change from Baseline indicated a better outcome. The ITT Population with no missing observations at Baseline and Week 8.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) and end of Main Portion (Week 8)

End point values	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: score on a scale				
least squares mean (standard error)	-0.144 ( $\pm$ 0.336)	-0.287 ( $\pm$ 0.398)		

## Statistical analyses

Statistical analysis title	Placebo vs Zilucoplan 0.3 mg/kg
Statistical analysis description: The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline MDAAT as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.	
Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.123
upper limit	0.837

## Secondary: Change From Baseline to Week 8 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score

End point title	Change From Baseline to Week 8 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Score
End point description: The FACIT-Fatigue Scale is a 13-item tool which measured an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue was measured on a 4-point Likert scale. The total FACIT-Fatigue Scale score for this study could range from 0-52, where 0 means the participants were very much fatigued during their usual daily activities and 52 means the participants were not at all fatigued during their usual daily activities. A negative change from Baseline indicated a worse outcome. The ITT Population with no missing observations at Baseline and Week 8.	
End point type	Secondary
End point timeframe: Baseline (Day 1) and end of Main Portion (Week 8)	

<b>End point values</b>	Placebo	Zilucoplan 0.3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	11		
Units: score on a scale				
least squares mean (standard error)	3.45 ( $\pm$ 3.41)	8.98 ( $\pm$ 4.08)		

## Statistical analyses

<b>Statistical analysis title</b>	Placebo vs Zilucoplan 0.3 mg/kg
Statistical analysis description:	
The p-value was based on a linear model with treatment and strata (anti-HMGCR+/anti-SRP+) as fixed factors with Baseline FACIT-Fatigue Scale as a covariate. The difference presented is zilucoplan 0.3 mg/kg minus placebo.	
Comparison groups	Placebo v Zilucoplan 0.3 mg/kg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.265
Method	Linear Mixed Effect Model
Parameter estimate	LS mean difference
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	15.55



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) to End of Safety Follow-up (Week 83)

Adverse event reporting additional description:

The Safety Population included all participants who have received at least 1 dose of study drug, with participants analyzed based on the actual study treatment received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Main Portion: Placebo
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Reporting group description:

Participants were randomized to receive daily SC doses of matching placebo during the 8-week Main Portion of the study.

Reporting group title	Main Portion: Zilucoplan 0.3 mg/kg
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Reporting group description:

Participants were randomized to receive daily SC doses of zilucoplan 0.3 mg/kg during the 8-week Main Portion of the study.

Reporting group title	Extension Portion: Zilucoplan 0.3 mg/kg
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Reporting group description:

Participants received daily SC doses of zilucoplan 0.3 mg/kg during the Extension Portion of the study.

Serious adverse events	Main Portion: Placebo	Main Portion: Zilucoplan 0.3 mg/kg	Extension Portion: Zilucoplan 0.3 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)	0 / 12 (0.00%)	8 / 25 (32.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (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
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (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
COVID-19			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	3 / 25 (12.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis bacterial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (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

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

<b>Non-serious adverse events</b>	Main Portion: Placebo	Main Portion: Zilucoplan 0.3 mg/kg	Extension Portion: Zilucoplan 0.3 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	9 / 12 (75.00%)	15 / 25 (60.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Injection site pruritus			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Injection site erythema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			

subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site bruise			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vaccination site pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Investigations			
Lipase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Amylase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Blood glucose increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 12 (0.00%) 0	3 / 25 (12.00%) 3
Skin procedural complication subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 12 (8.33%) 1	0 / 25 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 12 (0.00%) 0	0 / 25 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 5	4 / 12 (33.33%) 4	2 / 25 (8.00%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 12 (8.33%) 1	2 / 25 (8.00%) 2
Ear and labyrinth disorders Vertigo			

subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 12 (0.00%) 0	1 / 25 (4.00%) 1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 15 (20.00%)	3 / 12 (25.00%)	0 / 25 (0.00%)
occurrences (all)	3	3	0
Constipation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Faeces soft			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Dermatitis contact			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 12 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Intervertebral disc protrusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 12 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 12 (8.33%)	0 / 25 (0.00%)
occurrences (all)	0	1	0





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2021	<ul style="list-style-type: none"><li>- The Extension Portion was included in the Objectives and Endpoints table. Notes were added into the global protocol amendment that the long-term safety, tolerability, and efficacy were evaluated during the open-label Extension Portion of the study.</li><li>- Text regarding safety data review was updated.</li><li>- For France only, the duration of study participation during the Extension Portion of this study was amended from 4 months to 18 months.</li><li>- Added exclusion criterion 14 (hypersensitivity to investigational medicinal product [IMP]).</li><li>- Footnote "a" was updated to state that if a study participant permanently discontinued IMP treatment prior to the Week 8 Visit for any reason, he/she was not eligible for the Extension Portion. For study participants who permanently discontinued treatment with IMP, a Safety Follow-up Visit was performed 40 days after the last dose to collect information on any ongoing AEs or new serious adverse events since the last study visit.</li><li>- A new footnote "b" was added to the "Visits after Day Extension (E)117" to state that for France only, the duration of study participation during the Extension Portion included an open-label, single-arm, 18-month Treatment Period.</li><li>- Revised information on contraception.</li><li>- The objectives and endpoints were revised to reflect current UCB practices for the categorization and description of study objectives based on estimand definitions (to align with the updated ICH E9 [R1] addendum).</li><li>- The efficacy analysis presented in the protocol was updated from the 2-sided Wilcoxon rank sum test to the Van Elteren test, and a sentence was added to state that the effect of ZLP on ACR/EULAR minimal response was investigated using a binary logistic regression model with treatment and stratification included as factors.</li><li>- Provisions were included for the COVID-19 pandemic.</li><li>- Administrative updates.</li><li>- Changes were made to clarify that the snapshot was taken after the Week 8 Visit.</li></ul>

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.

The study was terminated based on the primary efficacy endpoint analysis after the first data lock.

Notes: