Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Crossover Study to Evaluate the Efficacy and Safety of LY3454738 in Adults with Chronic Spontaneous Urticaria Inadequately Controlled with H1-Antihistamines

Summary

EudraCT number	2019-002495-13
Trial protocol	DE
Global end of trial date	24 February 2021

Results information

Result version number	v1 (current)
This version publication date	02 March 2022
First version publication date	02 March 2022

Trial information

Trial identification

Sponsor protocol code	J1B-MC-FRCF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04159701
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 17480

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	24 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The reason for this study is to see if the study drug LY3454738 is safe and effective as treatment for participants with hives that are caused by chronic spontaneous urticaria (CSU) and that are not controlled with H1-antihistamines.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 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	United States: 43
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	52
EEA total number of subjects	9

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)	51
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

No Text Available

Period 1

Period 1 title	Period 1: Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence Group 1: (500 mg LY3454738, Placebo)

Arm description:

Participants received 500 mg LY3454738 intravenously (IV) every 2 weeks (Q2W) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	LY3454738
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV.

Arm title	Sequence Group 2: (Placebo, 500 mg LY3454738)

Arm description:

Participants received Placebo IV Q2W for 12 weeks.

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

Dosage and administration details:

Administered IV.

Number of subjects in period 1	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)
Started	39	13
Received at least one dose of study drug	39	13

Completed	31	12
Not completed	8	1
Study Terminated by sponsor	4	1
Consent withdrawn by subject	3	-
Pregnancy	1	-

Period 2	
Period 2 title	Washout Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator
Arms	
Are arms mutually exclusive?	Yes
Arm title	Sequence Group 1: (500 mg LY3454738, Placebo)
Arm description: Participants did not receive study drug.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Arm description: Participants did not receive study drug.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)
Started	31	12
Completed	18	8
Not completed	13	4
Study Terminated by sponsor	10	3
Consent withdrawn by subject	1	-
site terminated by sponsor	-	1
Miscellaneous	1	-
Inadvertent Enrollment	1	-

Period 3

Period 3 title	Period 2: Treatment Period (Crossover)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence Group 1: (500 mg LY3454738, Placebo)

Arm description:

Participants received Placebo IV Q2W for 12 weeks.

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

Dosage and administration details:

Administered IV.

Arm title	Sequence Group 2: (Placebo, 500 mg LY3454738)

Arm description:

Participants received 500 mg LY3454738 IV Q2W for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	LY3454738
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV.

Number of subjects in period 3	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)
Started	18	8
Completed	18	5
Not completed	0	3
Study Terminated by sponsor	-	2
Consent withdrawn by subject	-	1

Period 4	
Period 4 title	Post-treatment follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	No
Arm title	Sequence Group 1: (500 mg LY3454738, Placebo)

Arm description:

Participants did not receive study drug during the follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Sequence Group 2: (Placebo, 500 mg LY3454738)

Arm description:

Participants did not receive study drug during the follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)
Started	29	9
Completed	19	6
Not completed	10	3
Study Terminated by sponsor	6	3
Consent withdrawn by subject	3	-
Inadvertent Enrollment	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence Group 1: (500 mg LY3454738, Placebo)
Reporting group description:	
Participants received 500 mg LY3454738 intravenously (IV) every 2 weeks (Q2W) for 12 weeks.	
Reporting group title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Reporting group description:	
Participants received Placebo IV Q2W for 12 weeks.	

Reporting group values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)	Total
Number of subjects	39	13	52
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	38	13	51
>=65 years	1	0	1
Gender categorical Units: Subjects			
Female	30	11	41
Male	9	2	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	0	4
White	33	13	46
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
United States	33	10	43
Poland	5	1	6
Germany	1	2	3
Urticaria Activity Score Over 7 Days (UAS7) Score			
The baseline UAS7 is the sum of the daily UAS over the 7 days prior to the first treatment. A higher UAS or higher UAS7 indicates greater urticaria disease activity.			
Units: units on a scale			
arithmetic mean	26.51	24.26	
standard deviation	± 7.48	± 5.23	-

End points

End points reporting groups

Reporting group title	Sequence Group 1: (500 mg LY3454738, Placebo)
Reporting group description:	
Participants received 500 mg LY3454738 intravenously (IV) every 2 weeks (Q2W) for 12 weeks.	
Reporting group title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Reporting group description:	
Participants received Placebo IV Q2W for 12 weeks.	
Reporting group title	Sequence Group 1: (500 mg LY3454738, Placebo)
Reporting group description:	
Participants did not receive study drug.	
Reporting group title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Reporting group description:	
Participants did not receive study drug.	
Reporting group title	Sequence Group 1: (500 mg LY3454738, Placebo)
Reporting group description:	
Participants received Placebo IV Q2W for 12 weeks.	
Reporting group title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Reporting group description:	
Participants received 500 mg LY3454738 IV Q2W for 12 weeks.	

Reporting group title	Sequence Group 1: (500 mg LY3454738, Placebo)
Reporting group description:	
Participants did not receive study drug during the follow-up period.	
Reporting group title	Sequence Group 2: (Placebo, 500 mg LY3454738)
Reporting group description:	
Participants did not receive study drug during the follow-up period.	
Subject analysis set title	500 mg LY3454738
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 500 mg LY3454738 intravenously (IV) every 2 weeks (Q2W) for 12 weeks.	

Primary: Mean Change from Baseline in Urticaria Activity Score Over 7 Days (UAS7)

End point title	Mean Change from Baseline in Urticaria Activity Score Over 7 Days (UAS7)

End point description:

The UAS7 is the sum of the daily urticaria activity scores (UAS) over a 7-day period and ranges from 0 to 42. The daily UAS is the sum of the daily itch severity score (ISS) and daily number of hives score, and ranges from 0 to 6. The baseline UAS7 is the sum of the daily UAS over the 7 days prior to the first treatment. A higher UAS or higher UAS7 indicates greater urticaria disease activity. The ANCOVA model includes treatment as a factor and baseline UAS7 score in First 12-Week treatment period as covariates. Missing Week 12 scores will be imputed by carrying forward the participants' baseline scores (BOCF).

Analysis Population Description: All randomized participants who received at least one dose of study drug.

End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	13		
Units: units on a scale				
least squares mean (standard error)	-6.38 (± 1.645)	-9.32 (± 2.864)		

Statistical analyses

Statistical analysis title	UAS7
Comparison groups	Sequence Group 1: (500 mg LY3454738, Placebo) v Sequence Group 2: (Placebo, 500 mg LY3454738)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.73
upper limit	9.6

Secondary: Mean Change from Baseline in Itch Severity Score Over 7 Days (ISS7)

End point title	Mean Change from Baseline in Itch Severity Score Over 7 Days (ISS7)

End point description:

The ISS7 is the sum of the daily ISS over a 7-day period and ranges from 0 to 21. The daily ISS is the average of the morning and evening ISS on a 4-point scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The baseline ISS7 is the sum of the daily ISS over the 7 days prior to the first treatment. A higher ISS or higher ISS7 indicates more severe itching.The ANCOVA model includes treatment as a factor and baseline UAS7 score in First 12-Week treatment period as covariates. Missing Week 12 scores will be imputed by carrying forward the participants' baseline scores (BOCF).

Analysis Population Description: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	13		
Units: units on a scale				
least squares mean (standard error)	-2.91 (± 0.780)	-4.21 (± 1.367)		

Statistical analyses

Statistical analysis title	ISS7
Comparison groups	Sequence Group 1: (500 mg LY3454738, Placebo) v Sequence Group 2: (Placebo, 500 mg LY3454738)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	4.5

Secondary: Mean Change from Baseline in Hives Severity Score Over 7 Days (HSS7)

End point title	Mean Change from Baseline in Hives Severity Score Over 7 Days (HSS7)

End point description:

The HSS7 is the sum of the daily number of hives over a 7-day period and ranges from 0 to 21. The daily number of hives score (also called HSS) is the average of the morning and evening number of hive scores on a four-point
scale of 0 (none), 1 (between 1 and 6 hives, inclusive), 2 (between 7 and 12 hives, inclusive), and 3 (greater than 12 hives). The baseline weekly HSS7 is the sum of the HSS over the 7 days prior to the first treatment. A higher HSS or higher HSS7 indicates a greater number of hives. The ANCOVA model includes treatment as a factor and baseline UAS7 score in First 12-Week treatment period as covariates. Missing Week 12 scores will be imputed by carrying forward the participants' baseline scores (BOCF).

Analysis Population Description: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	13		
Units: units on a scale				
least squares mean (standard error)	-3.45 (± 0.931)	-5.17 (± 1.631)		

Statistical analyses

Statistical analysis title	HSS7
Comparison groups	Sequence Group 1: (500 mg LY3454738, Placebo) v Sequence Group 2: (Placebo, 500 mg LY3454738)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.369
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.09
upper limit	5.53

Secondary: Percentage of Participants Achieving Urticaria Activity Score Over 7 Days (UAS7) ≤6 (Stratified by baseline UAS7 (< 28 vs >= 28) score)

End point title	Percentage of Participants Achieving Urticaria Activity Score Over 7 Days (UAS7) ≤6 (Stratified by baseline UAS7 (< 28 vs >= 28) score)

End point description:

The UAS7 is the sum of the daily urticaria activity scores (UAS) over a 7-day period and ranges from 0 to 42. The daily UAS is the sum of the daily itch severity score (ISS) and daily number of hives score, and ranges from 0 to 6. The baseline UAS7 is the sum of the daily UAS over the 7 days prior to the first treatment. A higher UAS or higher UAS7 indicates greater urticaria disease activity.

Analysis Population Description: All randomized participants who received at least one dose of study drug and had UAS7 ≤6.

End point type	Secondary

End point timeframe:

Week 12

End point values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	13		
Units: percentage of participants				
number (not applicable)	15.4	23.1		

Statistical analyses

Statistical analysis title	UAS7
Statistical analysis description:	
Cochran-Mantel-Haenszel (CMH) test adjusted by baseline UAS7 (< 28 vs >= 28) score.	
Comparison groups	Sequence Group 1: (500 mg LY3454738, Placebo) v Sequence Group 2: (Placebo, 500 mg LY3454738)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	2.7

Secondary: Percentage of Participants Achieving Urticaria Activity Score Over 7 Days (UAS7) ≤6 (Stratified by baseline UAS7 (< median vs >= median) Score)

End point title	Percentage of Participants Achieving Urticaria Activity Score Over 7 Days (UAS7) ≤6 (Stratified by baseline UAS7 (< median vs >= median) Score)

End point description:

The UAS7 is the sum of the daily urticaria activity scores (UAS) over a 7-day period and ranges from 0 to 42.The daily UAS is the sum of the daily itch severity score (ISS) and daily number of hives score, and ranges from 0 to 6. The baseline UAS7 is the sum of the daily UAS over the 7 days prior to the first treatment. A higher UAS or higher UAS7 indicates greater urticaria disease activity.

Analysis Population Description: All randomized participants who received at least one dose of study drug and had UAS7 ≤6.

End point type	Secondary

End point timeframe:

Week 12

End point values	Sequence Group 1: (500 mg LY3454738, Placebo)	Sequence Group 2: (Placebo, 500 mg LY3454738)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	13		
Units: percentage of participants				
number (not applicable)	15.4	23.1		

Statistical analyses

Statistical analysis title	UAS7
Statistical analysis description:	
Cochran-Mantel-Haenszel (CMH) test adjusted by baseline UAS7 (< median vs >= median) score.	
Comparison groups	Sequence Group 1: (500 mg LY3454738, Placebo) v Sequence Group 2: (Placebo, 500 mg LY3454738)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.674
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	2.68

Secondary: Pharmacokinetics (PK): Area Under the Concentration Versus Time Curve From Time Zero to 336 Hours (AUC [0-336h]) of LY3454738

End point title	Pharmacokinetics (PK): Area Under the Concentration Versus Time Curve From Time Zero to 336 Hours (AUC [0-336h]) of LY3454738

End point description:

Pharmacokinetics (PK): Area Under the Concentration Versus Time Curve From Time Zero to 336 Hours (AUC [0-336h]) of LY3454738

Analysis Population Description: All randomized participants who received at least one dose of LY3454738 and had evaluable PK data.

End point type	Secondary

End point timeframe:

Before Infusion, after infusion, 1 hour after infusion and 2 hours after infusion on Day 1; Before Infusion on Day 8, 15, 29, 43, 57, 71, 85, 92, 99, 113, 127, 141, 155, 169 and Post-Treatment Follow-up

End point values	500 mg LY3454738			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: micrograms*hour per milliliter(ug*h/mL)				
geometric mean (geometric coefficient of variation)	53400 (± 49)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Concentration (Cmax) of LY3454738

End point title	PK: Maximum Concentration (Cmax) of LY3454738

End point description:

PK: Maximum Concentration (Cmax) of LY3454738

Analysis Population Description: All randomized participants who received at least one dose of LY3454738 and had evaluable PK data.

End point type	Secondary

End point timeframe:

Before Infusion, after infusion, 1 hour after infusion and 2 hours after infusion on Day 1; Before Infusion on Day 8, 15, 29, 43, 57, 71, 85, 92, 99, 113, 127, 141, 155, 169 and Post-Treatment Follow-up

End point values	500 mg LY3454738			
Subject group type	Subject analysis set			
Number of subjects analysed	44			
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)	256 (± 30.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline Up To 28 Weeks	
Adverse event reporting additional description:	
All participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	500 mg LY3454738_First 12-Week Period
Reporting group description:	
Participants received 500 mg LY3454738 IV Q2W for 12 weeks.	
Reporting group title	Placebo_First 12-Week Period
Reporting group description:	
Participants received Placebo IV Q2W for 12 weeks.	
Reporting group title	500 LY3454738_Second 12-Week Crossover Period
Reporting group description:	
Participants received 500 mg LY3454738 IV Q2W for 12 weeks.	
Reporting group title	Placebo_Second 12-Week Crossover Period
Reporting group description:	
Participants received Placebo IV Q2W for 12 weeks.	
Reporting group title	Follow-Up Period
Reporting group description:	
Participants did not receive study drug during the follow-up period.	

Serious adverse events	500 mg LY3454738_First 12-Week Period	Placebo_First 12-Week Period	500 LY3454738_Second 12-Week Crossover Period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo_Second 12-Week Crossover Period	Follow-Up Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	500 mg LY3454738_First 12-Week Period	Placebo_First 12-Week Period	500 LY3454738_Second 12-Week Crossover Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	4 / 13 (30.77%)	1 / 8 (12.50%)
Investigations			
blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
haematocrit decreased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
haemoglobin decreased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 39 (2.56%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
hypoaesthesia			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 39 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
migraine			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
sensation of foreign body			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
eczema eyelids			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 39 (2.56%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
dyspepsia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
dysphagia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
nausea			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
bipolar disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 39 (5.13%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
pain in extremity			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
otitis media			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
post procedural infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
urinary tract infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 39 (0.00%)	1 / 13 (7.69%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
metabolic acidosis			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 39 (0.00%)	0 / 13 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo_Second 12-Week Crossover Period	Follow-Up Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	2 / 38 (5.26%)	
Investigations			
blood creatine phosphokinase increased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
haematocrit decreased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
haemoglobin decreased			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
headache			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	3 / 18 (16.67%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
hypoaesthesia			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
migraine			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
sensation of foreign body			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
eczema eyelids			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	2 / 18 (11.11%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
dyspepsia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
dysphagia			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
nausea			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed	2 / 18 (11.11%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
bipolar disorder			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
pain in extremity			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	2 / 38 (5.26%)	
occurrences (all)	1	2	
otitis media			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
post procedural infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	0 / 18 (0.00%)	0 / 38 (0.00%)	
occurrences (all)	0	0	
urinary tract infection			
alternative dictionary used: MedDRA 24.0			
subjects affected / exposed	1 / 18 (5.56%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 24.0			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 38 (0.00%) 0	
Metabolism and nutrition disorders metabolic acidosis alternative dictionary used: MedDRA 24.0 subjects affected / exposed occurrences (all)	 1 / 18 (5.56%) 1	 0 / 38 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2020	Changes to inclusion and exclusion (I/E) and criteria for withholding and discontinuing treatment were made to minimize risks of enrolling or dosing patients with COVID-19.

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 for lack of efficacy after an interim analysis was performed.

Notes: