Clinical trial results:
A Phase 2 Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Dose Levels of Subcutaneously Administered ELX-02 in Patients with Cystic Fibrosis with at Least One G542X Allele

Summary

EudraCT number	2018-000966-12
Trial protocol	DE
Global end of trial date	05 April 2022

Results information

Result version number	v1 (current)
This version publication date	27 May 2023
First version publication date	27 May 2023

Trial information

Trial identification

Sponsor protocol code	EL-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04126473
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eloxx Pharmaceuticals, Inc.
Sponsor organisation address	480 Arsenal Way, Suite 130, Watertown, MA, United States, 02472
Public contact	Tim Kachmar, Eloxx Pharmaceuticals, Inc., +1 6176459926, tim.kachmar@eloxxpharma.com
Scientific contact	Tim Kachmar, Eloxx Pharmaceuticals, Inc., +1 6176459926, tim.kachmar@eloxxpharma.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	05 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of different dose levels and exposures of ELX-02 administered subcutaneously (SC), as monotherapy and in combination with ivacaftor in subjects with Cystic Fibrosis (CF) carrying at least one G542X or phenotypically similar Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) nonsense allele and to study the pharmacokinetics (PK) of multiple SC doses of ELX-02 as monotherapy and in combination with ivacaftor, in subjects with CF.

Protection of trial subjects:

The study was conducted in compliance with the study protocol, with the International Standard of Good Clinical Practice (GCP) procedures, and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 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	Israel: 12
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	17
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)	17

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 centers: 4 in Israel and 2 in Germany from 05 November 2019 to 05 April 2022.

Pre-assignment

Screening details:

A total of 17 subjects were enrolled in this study. The study consisted of 3 periods for each subject; a screening period of up to 6 weeks, a treatment period (TP) of up to 10 weeks and a safety follow up period of 4 weeks after the last treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ELX-02: All Subjects (At least one TP from TP 1 to TP 5)

Arm description:

Subjects received ELX-02 0.3, 0.75 and 1.5 milligram per kilograms (mg/kg) subcutaneously (SC) daily for one week each in Treatment Periods 1,2 and 3 as monotherapy and ELX-02 up to 3.0 mg/kg SC daily for 2 weeks in Treatment Period 4 (individualized dose 2.8 mg/kg to 3.0 mg/kg to target a total exposure of approximately 190 microgram-hours per milliliter (mcg*h/mL). Subjects received 5 ELX-02 1.5 mg/kg for 1 week, followed by ELX-02 at 1.5 mg/kg SC daily, together with one ivacaftor 150 mg tablet orally every 12 hours for 4 weeks in Treatment Period 5.

Arm type	Experimental
Investigational medicinal product name	ELX-02
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ELX-02 0.3, 0.75 or 1.5 mg/kg SC daily for one week in Treatment Periods 1, 2 and 3, respectively. ELX-02 was dosed daily for 2 weeks in Treatment Period 4 with an individualized dose 2.8 mg/kg to 3.0 mg/kg to target a total exposure of approximately 190 mcg*h/mL. In Treatment Period 5, ELX-02 was dosed at 1.5 mg/kg daily for one week followed by ELX-02 at 1.5 mg/kg daily in combination with one ivacaftor 150 mg tablet every 12 hours for 4 weeks.

Investigational medicinal product name	Ivacaftor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivacaftor administered orally in Treatment Period 5 as 150 mg tablet every 12 hours together with ELX-02 at 1.5 mg/kg SC daily for 4 weeks after administration of ELX-02 as monotherapy at a dose of 1.5 mg/kg (as in Treatment Period 3) for 1 week.

Number of subjects in period 1	ELX-02: All Subjects (At least one TP from TP 1 to TP 5)
Started	17
Completed	11
Not completed	6
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Subjects received ELX-02 0.3, 0.75 and 1.5 milligram per kilograms (mg/kg) subcutaneously (SC) daily for one week each in Treatment Periods 1,2 and 3 as monotherapy and ELX-02 up to 3.0 mg/kg SC daily for 2 weeks in Treatment Period 4 (individualized dose 2.8 mg/kg to 3.0 mg/kg to target a total exposure of approximately 190 microgram-hours per milliliter (mcg*h/mL). Subjects received 5 ELX-02 1.5 mg/kg for 1 week, followed by ELX-02 at 1.5 mg/kg SC daily, together with one ivacaftor 150 mg tablet orally every 12 hours for 4 weeks in Treatment Period 5.	

Reporting group values	Overall trial	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 29.4 ± 8.95	 -	
Gender categorical Units: Subjects			
Female	5	5	
Male	12	12	
Race Units: Subjects			
Black or African American	0	0	
White	17	17	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	17	17	

End points

End points reporting groups

Reporting group title	ELX-02: All Subjects (At least one TP from TP 1 to TP 5)

Reporting group description:

Subjects received ELX-02 0.3, 0.75 and 1.5 milligram per kilograms (mg/kg) subcutaneously (SC) daily for one week each in Treatment Periods 1,2 and 3 as monotherapy and ELX-02 up to 3.0 mg/kg SC daily for 2 weeks in Treatment Period 4 (individualized dose 2.8 mg/kg to 3.0 mg/kg to target a total exposure of approximately 190 microgram-hours per milliliter (mcg*h/mL). Subjects received 5 ELX-02 1.5 mg/kg for 1 week, followed by ELX-02 at 1.5 mg/kg SC daily, together with one ivacaftor 150 mg tablet orally every 12 hours for 4 weeks in Treatment Period 5.

Subject analysis set title	Treatment Period 1: ELX-02 0.3 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received ELX-02 0.3 mg/kg SC daily for 1 week (about 0.4 mL/day, total dose not to exceed 2.1 mg/kg for this 7-day period) in Treatment Period 1. Safety population consisted of all treated subjects who received at least one dose of study medication, including subjects prematurely withdrawn from the study.

Subject analysis set title	Treatment Period 2: ELX-02 0.75 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received ELX-02 0.75 mg/kg SC daily for 1 week (about 0.9 mL/day, total dose not to exceed 5.25 mg/kg for this 7-day period) in Treatment Period 2.

Subject analysis set title	Treatment Period 3: ELX-02 1.5 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received ELX-02 1.5 mg/kg SC daily for 1 week (two daily injections of about 0.9 mL, total dose not to exceed 10.5 mg/kg for this 7-day period) in Treatment Period 3.

Subject analysis set title	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received ELX-02 individualized doses 2.8 mg/kg to 3.0 mg/kg SC daily for 2 weeks (up to 3 or 4 injections of about 1.2 mL) to target a total exposure of approximately 190 mcg*h/mL in Treatment Period 4.

Subject analysis set title	Treatment Period 5: ELX-02 + Ivacaftor
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received ELX-02 1.5 mg/kg (as in Treatment Period 3) for 1 week, followed by 4 weeks of therapy with ELX-02 1.5 mg/kg SC daily, together with Ivacaftor 150 mg tablet taken orally every 12 hours in Treatment Period 5.

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Severe TEAEs, Serious TEAEs, Related TEAEs, Related Serious TEAE, TEAE Leading to Study Drug Discontinuation and Death

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs), Severe TEAEs, Serious TEAEs, Related TEAEs, Related Serious TEAE, TEAE Leading to Study Drug Discontinuation and Death[1]

End point description:

TEAE was defined as any AE with onset after the first administration of study medication through the end of the study, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. Severe TEAE is a TEAE with CTCAE Grade 3 or above. Related TEAE is defined as a TEAE with a certain, probable/likely, or possible relationship to the study drug. SAE was an AE resulting in any of the following outcomes or

deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening. The Safety population comprised of all subjects who received 1 or more doses of study medication. Serious TEAE subject identified 3 months after completing treatment period 3 during dosing hiatus.

End point type	Primary

End point timeframe:

From baseline up to 29 months

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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	8	4
Units: subjects				
All TEAE	7	6	4	4
Severe TEAE	0	0	0	0
Serious TEAE	0	0	1	0
Related TEAE	6	5	4	2
Related Serious TEAE	0	0	0	0
TEAE Leading to Study Drug Discontinuation	1	1	0	0
TEAE Leading to Death	0	0	0	0

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: subjects				
All TEAE	5			
Severe TEAE	1			
Serious TEAE	0			
Related TEAE	1			
Related Serious TEAE	0			
TEAE Leading to Study Drug Discontinuation	1			
TEAE Leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-24h): Area Under the Plasma Concentration-time Curve from Time 0

to 24 Hours Postdose for ELX-02

End point title	AUC(0-24h): Area Under the Plasma Concentration-time Curve from Time 0 to 24 Hours Postdose for ELX-02[2]

End point description:

AUC(0-24h) was defined as the area under the plasma concentration-time curve from zero to the time of the last measured concentration that is 24 hours above the limit of quantification post dose. The PK population included all safety subjects who had analyzable PK data without relevant deviation interfering with the PK evaluations. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint. '99999' indicates that data could not be estimated for specified Treatment Period where data is not available due to either no value(s) within the detectable range or no sample(s) were collected.

End point type	Primary

End point timeframe:

Treatment Period 1-4 (Day 1) and Treatment Period 5 (Day 8): Pre-dose, and at 15 minutes, 30 minutes, 1,3,4,6,8, and 24 hours post-dose

Notes:

[2] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	2	2
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	99999 (± 99999)	99999 (± 99999)	26729.645 (± 8280.6357)	31301.081 (± 5781.1191)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: Ae24h: Amount Excreted in Urine from Time 0 to 24 Hours Postdose ELX-02

End point title	Ae24h: Amount Excreted in Urine from Time 0 to 24 Hours Postdose ELX-02[3]

End point description:

Ae24h was the amount of study drug excreted in urine from Time 0 to 24 Hours post dose. The PK

population included all safety subjects who had analyzable PK data without relevant deviation interfering with the PK evaluations. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint. Urine PK was not collected during Treatment Period 5.

End point type	Primary

End point timeframe:

Treatment Period 1-4: pre-dose, and at 0-8 hours, and 8-24 hours post-dose

Notes:

[3] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	8	3
Units: milligram (mg)				
arithmetic mean (standard deviation)	22.043 (± 10.8882)	49.499 (± 14.6477)	106.350 (± 59.3726)	173.822 (± 90.9374)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	0[4]			
Units: milligram (mg)				
arithmetic mean (standard deviation)	()			

Notes:

[4] - Urine PK was not collected during Treatment Period 5.

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration for ELX-02

End point title	Cmax: Maximum Observed Plasma Concentration for ELX-02[5]

End point description:

Cmax was defined as the maximum observed plasma concentration. PK population included all safety subjects who had analyzable PK data without relevant deviation interfering with the PK evaluations. Here, overall number of subjects analyzed signifies subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Treatment Period 1- 4 (Day 1) and Treatment Period 5 (Day 8): pre-dose and at 15 minutes, 30 minutes, 1, 3, 4, 6, 8 and 24 hours post-dose

Notes:

[5] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	8	4
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	1066.7 (± 187.71)	2286.0 (± 551.53)	4775.0 (± 1099.73)	8632.5 (± 243.91)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	5265.0 (± 777.88)			

Statistical analyses

No statistical analyses for this end point

Primary: Cpeak: Maximum (Peak)- Concentration in Plasma at Expected Time of Maximum Concentration (Cpeak) for ELX-02

End point title	Cpeak: Maximum (Peak)- Concentration in Plasma at Expected Time of Maximum Concentration (Cpeak) for ELX-02[6]

End point description:

Cpeak was defined as the highest level of drug concentration in plasma at expected time of maximum concentration (peak) at defined timepoints. The PK population included all safety subjects who had analyzable PK data without relevant deviation interfering with the PK evaluations. Here, "n" refers to the subjects who were evaluable for specified categories of this endpoint. Cpeak was not evaluated at treatment period 5. '99999' indicates that data could not be estimated for specified Treatment Period where data is not available due to either no value(s) within the detectable range or no sample(s) were collected.

End point type	Primary

End point timeframe:

Treatment Period 1-4 (Day 7): at 30 minutes and 1 hour post dose, Treatment Period 4 (Day 14): at 30 minutes and 1 hour post dose

Notes:

[6] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	8	4
Units: ng/mL				

arithmetic mean (standard deviation)				
Cpeak at Day 7 (n=12,9,7,4,0)	1014.2 (± 164.81)	2632.2 (± 562.49)	3978.6 (± 1113.39)	8092.5 (± 1937.34)
Cpeak at Day 14 (n=0,0,0,4,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	7187.5 (± 3079.91)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	0[7]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cpeak at Day 7 (n=12,9,7,4,0)	()			
Cpeak at Day 14 (n=0,0,0,4,0)	()			

Notes:

[7] - Cpeak was not evaluated at treatment period 5.

Statistical analyses

No statistical analyses for this end point

Primary: Cpredose: Pre-dose Observed Plasma Concentrations Over Time for ELX-02

End point title	Cpredose: Pre-dose Observed Plasma Concentrations Over Time for ELX-02[8]

End point description:

Cpredose was defined as Trough plasma concentration observed at the end of the dosing interval (that is (i.e.), at each predose starting from second dose) at defined timepoints. The PK population included all safety subjects who had analyzable PK data without relevant deviation interfering with the PK evaluations. Here, number of subjects analyzed signifies subjects who were evaluable for this endpoint. Here, "n" refers to the subjects who were evaluable for specified categories of this endpoint. '99999' indicates that data could not be estimated for specified Treatment Period where data is not available due to either no value(s) within the detectable range or no sample(s) were collected.

End point type	Primary

End point timeframe:

Treatment Period 1-4: pre-dose on Days 1 and 7; Treatment Period 4: pre-dose on Day 14; Treatment Period 5: pre-dose on Days 8,14,21 and 35

Notes:

[8] - 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: Descriptive statistics were performed; no inferential statistical analyses were performed.

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	8	4
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Predose at Day 1 (n=13,9,8,4,0)	0.00 (± 0.000)	0.00 (± 0.000)	427.50 (± 1209.153)	0.00 (± 0.000)

Predose at Day 7 (12,10,8,4,0)	0.00 (± 0.000)	0.00 (± 0.000)	6.90 (± 7.793)	17.65 (± 5.606)
Predose at Day 8 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Predose at Day 14 (n=0,0,0,4,3)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	20.42 (± 2.502)
Predose at Day 21 (n=0,0,0,0,3)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Predose at Day 35 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Predose at Day 1 (n=13,9,8,4,0)	99999 (± 99999)			
Predose at Day 7 (12,10,8,4,0)	99999 (± 99999)			
Predose at Day 8 (n=0,0,0,0,4)	27.53 (± 15.250)			
Predose at Day 14 (n=0,0,0,4,3)	13.60 (± 11.789)			
Predose at Day 21 (n=0,0,0,0,3)	34.13 (± 34.240)			
Predose at Day 35 (n=0,0,0,0,4)	18.05 (± 27.093)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Sweat Chloride Concentration

End point title	Change from Baseline in Sweat Chloride Concentration

End point description:

Change from Baseline in Sweat Chloride Concentration were calculated from defined timepoints and reported in this endpoint. Here, "number of subjects analysed signifies" subjects who were evaluable for this endpoint and "n" refers to the subjects who were evaluable for specified categories of this endpoint. '99999' indicates no samples were collected.

End point type	Secondary

End point timeframe:

Baseline, Treatment Period 1 to 5 (Day 1): pre-dose, Treatment Period 1 to 5 (Day 7): 6 hours post-dose, Treatment Period 4 to 5 (Day 14): 6 hours post-dose, Treatment Period 5 (Days 8, 21, 28, and 35): 6 hours post-dose

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	8	7	4
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,8,7,4,1)	99999 (± 99999)	-4.86 (± 14.725)	-3.84 (± 8.474)	-2.27 (± 5.132)
Change at Day 7 (n=10,7,7,4,4)	1.03 (± 6.362)	-1.70 (± 9.141)	-4.99 (± 10.230)	3.85 (± 7.341)
Change at Day 8 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 14 (n=0,0,0,4,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	4.23 (± 5.616)
Change at Day 21 (n=0,0,0,0,3)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 28 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 35 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,8,7,4,1)	1.50 (± 99999)			
Change at Day 7 (n=10,7,7,4,4)	0.55 (± 2.505)			
Change at Day 8 (n=0,0,0,0,4)	-1.70 (± 2.482)			
Change at Day 14 (n=0,0,0,4,4)	4.80 (± 4.774)			
Change at Day 21 (n=0,0,0,0,3)	1.57 (± 2.113)			
Change at Day 28 (n=0,0,0,0,4)	-0.82 (± 9.378)			
Change at Day 35 (n=0,0,0,0,4)	-0.20 (± 7.445)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percent Predicted Forced Expiratory Volume (ppFEV1)

End point title	Change from Baseline in Percent Predicted Forced Expiratory Volume (ppFEV1)

End point description:

FEV1 was measured as the volume of air that was forcibly blown out in one second, after full inspiration.

These were preferably performed pre-bronchodilator, ideally at the same time at every study visit. If not performed pre-bronchodilator, it was to be performed consistently post-bronchodilator at each study visit. Here, "number of subjects analysed signifies" subjects who were evaluable for this endpoint and "n" refers to the subjects who were evaluable for specified categories of this endpoint. '99999' indicates no samples were collected.

End point type	Secondary

End point timeframe:

Baseline, Treatment Period 1-5: Day 1, Day 7, Treatment Period 4-5: Day 14 and Treatment Period 5: Days 8, 21, 28 and 35

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	10	8	4
Units: Percentage of predicted FEV1				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,10,8,4,1)	99999 (± 99999)	1.1 (± 4.48)	-0.5 (± 6.91)	3.8 (± 5.91)
Change at Day 7 (n=13,9,8,4,1)	0.2 (± 4.25)	0.4 (± 6.44)	0.1 (± 5.99)	3.5 (± 5.92)
Change at Day 8 (n=0,0,0,0,5)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 14 (n=0,0,0,4,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	46.8 (± 18.89)
Change at Day 21 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 28 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 35 (n=0,0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage of predicted FEV1				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,10,8,4,1)	1.0 (± 99999)			
Change at Day 7 (n=13,9,8,4,1)	-0.2 (± 9.09)			
Change at Day 8 (n=0,0,0,0,5)	-1.8 (± 3.03)			
Change at Day 14 (n=0,0,0,4,4)	0.0 (± 5.89)			
Change at Day 21 (n=0,0,0,0,4)	-4.8 (± 10.47)			
Change at Day 28 (n=0,0,0,0,4)	-2.8 (± 6.24)			
Change at Day 35 (n=0,0,0,0,6)	-1.3 (± 2.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percent Predicted Forced Vital Capacity (ppFVC)

End point title	Change from Baseline in Percent Predicted Forced Vital Capacity (ppFVC)

End point description:

FVC was pulmonary function test and was conducted as per the study Pulmonary Function Manual, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement. FVC was the maximum amount of air exhaled from the lungs after taking the deepest breath possible. The highest value was recorded into a spirometer. Here, "n" refers to the subjects who were evaluable for specified categories of this endpoint. '99999' indicates no samples were collected.

End point type	Secondary

End point timeframe:

Baseline, Treatment Period 1-5: Day 1, Day 7, Treatment Period 4-5: Day 14 and Treatment Period 5: Days 8, 21, 28 and 35

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	10	8	4
Units: Percentage of predicted FCV				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,10,8,4,1)	99999 (± 99999)	1.2 (± 8.07)	1.3 (± 9.13)	3.8 (± 3.77)
Change at Day 7 (n=13,9,8,4,5)	-0.2 (± 3.67)	1.1 (± 8.68)	0.5 (± 7.05)	1.5 (± 2.52)
Change at Day 8 (n=0,0,0,0,5)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 14 (n=0,0,0,4,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-1.5 (± 7.59)
Change at Day 21 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 28 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 35 (n=0,0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Treatment Period 5: ELX-02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage of predicted FCV				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,10,8,4,1)	0.0 (± 99999)			
Change at Day 7 (n=13,9,8,4,5)	-2.4 (± 6.91)			
Change at Day 8 (n=0,0,0,0,5)	-1.6 (± 3.36)			

Change at Day 14 (n=0,0,0,4,4)	0.0 (± 5.35)			
Change at Day 21 (n=0,0,0,0,4)	-4.8 (± 8.92)			
Change at Day 28 (n=0,0,0,0,4)	-2.0 (± 3.92)			
Change at Day 35 (n=0,0,0,0,6)	-0.5 (± 2.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Percent Predicted Forced Expiratory Flow at 25-75% (ppFEF25-75)

End point title	Change from Baseline in Percent Predicted Forced Expiratory Flow at 25-75% (ppFEF25-75)

End point description:

Forced expiratory flow at 25-75% [FEF25-75]) was defined as how much air a person exhaled during a forced breath, measured using standard spirometry techniques. Here, "number of subjects analysed signifies" subjects who were evaluable for this endpoint and "n" refers to the subjects who were evaluable for specified categories of this endpoint. '99999' indicates no samples were collected.

End point type	Secondary

End point timeframe:

Baseline, Treatment Period 1-5: Day 1, Day 7, Treatment Period 4-5: Day 14 and Treatment Period 5: Days 8, 21, 28 and 35

End point values	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: ELX-02 1.5 mg/kg	Treatment Period 4: An individualized dose up to 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	9	7	3
Units: Percentage of predicted FEF25-75				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,9,7,3,1)	99999 (± 99999)	0.113 (± 0.438)	0.001 (± 0.364)	0.280 (± 0.305)
Change at Day 7 (n=12,8,7,3,5)	-0.015 (± 0.287)	0.063 (± 0.234)	0.036 (± 0.294)	0.340 (± 0.344)
Change at Day 8 (n=0,0,0,0,5)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 14 (n=0,0,0,3,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	0.300 (± 0.249)
Change at Day 21 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 28 (n=0,0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Change at Day 35 (n=0,0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Treatment Period 5: ELX-			

	02 + Ivacaftor			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage of predicted FEF25-75				
arithmetic mean (standard deviation)				
Change at Day 1 (n=0,9,7,3,1)	0.550 (± 99999)			
Change at Day 7 (n=12,8,7,3,5)	0.142 (± 0.608)			
Change at Day 8 (n=0,0,0,0,5)	-0.120 (± 0.206)			
Change at Day 14 (n=0,0,0,3,4)	-0.047 (± 0.396)			
Change at Day 21 (n=0,0,0,0,4)	-0.215 (± 0.680)			
Change at Day 28 (n=0,0,0,0,4)	-0.198 (± 0.650)			
Change at Day 35 (n=0,0,0,0,6)	-0.203 (± 0.460)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 29 months

Adverse event reporting additional description:

Safety population consisted of all treated subjects who received at least one dose of study medication, including subjects prematurely withdrawn from the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Treatment Period 1: ELX-02 0.3 mg/kg

Reporting group description:

Subjects received ELX-02 0.3 mg/kg SC daily for 1 week (about 0.4 mL/day, total dose not to exceed 2.1 mg/kg for this 7-day period) in Treatment Period 1. Safety population consisted of all treated subjects who received at least one dose of study medication, including subjects prematurely withdrawn from the study.

Reporting group title	Treatment Period 2: ELX-02 0.75 mg/kg

Reporting group description:

Subjects received ELX-02 0.75 mg/kg SC daily for 1 week (about 0.9 mL/day, total dose not to exceed 5.25 mg/kg for this 7-day period) in Treatment Period 2.

Reporting group title	Treatment Period 3: 1.5 mg/kg

Reporting group description:

Subjects received ELX-02 1.5 mg/kg SC daily for 1 week (two daily injections of about 0.9 mL, total dose not to exceed 10.5 mg/kg for this 7-day period) in Treatment Period 3.

Reporting group title	Treatment Period 4: 3 mg/kg

Reporting group description:

Subjects received ELX-02 individualized doses 2.8 mg/kg to 3.0 mg/kg SC daily for 2 weeks (up to 3 or 4 injections of about 1.2 mL) to target a total exposure of approximately 190 mcg*h/mL in Treatment Period 4.

Reporting group title	Treatment Period 5: ELX-02 + Ivacaftor

Reporting group description:

Subjects received ELX-02 1.5 mg/kg (as in Treatment Period 3) for 1 week, followed by 4 weeks of therapy with ELX-02 1.5 mg/kg SC daily, together with Ivacaftor 150 mg tablet taken orally every 12 hours in Treatment Period 5.

Serious adverse events	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: 1.5 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric	Additional description: Serious TEAE subject identified 3 months after completing treatment period 3 during dosing hiatus.		

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer	Additional description: Serious TEAE subject identified 3 months after completing treatment period 3 during dosing hiatus.		
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Period 4: 3 mg/kg	Treatment Period 5: ELX-02 + Ivacaftor	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric	Additional description: Serious TEAE subject identified 3 months after completing treatment period 3 during dosing hiatus.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer	Additional description: Serious TEAE subject identified 3 months after completing treatment period 3 during dosing hiatus.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment Period 1: ELX-02 0.3 mg/kg	Treatment Period 2: ELX-02 0.75 mg/kg	Treatment Period 3: 1.5 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	6 / 10 (60.00%)	4 / 8 (50.00%)
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	3 / 13 (23.08%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	5	1	2
Injection site erythema			

subjects affected / exposed	0 / 13 (0.00%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Injection site swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Injection site oedema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Injection site induration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Injection site haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site dryness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injection site pruritus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injection site vesicles			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sputum increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tympanometry abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	4	0	0
Ear pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Vertigo			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	3
Skin induration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	1 / 8 (12.50%)
occurrences (all)	6	0	1
Bacterial disease carrier			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Influenza			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Treatment Period 4: 3 mg/kg	Treatment Period 5: ELX-02 + Ivacaftor	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 6 (83.33%)	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site swelling			

subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injection site oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site induration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site dryness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site reaction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Injection site vesicles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Allergy to animal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Sputum increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Tympanometry abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Ear pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin induration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Bacterial disease carrier			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2019	Amendment 1.0: 1) Updated the nonclinical and clinical safety information (based on studies that had been completed since the original version was submitted). 2) Further defined and clarified the objectives and endpoints. 3) Updated the description of the study design to more clearly delineate how the subjects will progress through the study. 4) Provided a clear justification on the rationale for the recommended doses, duration of study drug administration, and the modification of the dosing regimen from twice weekly to daily. 5) Modified number of subjects to permit intra-subject dose escalation. 6) Adjusted the inclusion/exclusion criteria to provide clarity as to the nonsense alleles most appropriate for treatment with the investigational product under study, increased age of entry from 16 to 18 in Germany, as well as more clearly defining the original criteria. 7) Enhanced and provided additional guidance on the protocol defined stopping rules. 8) Reduced subject burden by simplifying procedures, modifying the PK schedule, decrease in-patient hospital stays, as well as offering an optional hiatus between treatment periods. 9) Additional changes to provide clarity, correct errors, and additional detail for certain sections were also made in order to increase the understanding of the protocol.
14 February 2020	Amendment 2.0: 1) Modified number of homozygous subjects to reflect actual availability of these subjects and to further define the type of heterozygous subjects to be allowed in the study. 2) Clarified the return from hiatus procedures. 3) Enhanced and provided additional guidance on the protocol defined stopping rules. 4) Reduced subject burden by simplifying procedures. 5) Removed exploratory objectives/endpoints that were no longer to be evaluated in this study. 6) Additional changes to provide clarity, correct errors, and additional detail for certain sections were also made in order to increase the understanding of the protocol.
06 October 2020	Amendment 3.0: Permitted subjectss to be enrolled into the study with F508del mutation on the second allele only if not receiving any CFTR modulators or potentiators for 2 months prior to study treatment.
12 November 2020	Amendment 4.0: Included measures taken to accommodate COVID-19 pandemic situation in the protocol.
27 January 2021	Amendment 4.1: Israel specific changes: 1) Added Treatment Period 5 – ELX-02 1.5mg/kg in combination with ivacaftor 150 mg twice daily for 28 days. 2) Provided rationale for the combined therapy in Treatment Period 5. 3) Provided support for 28 days administration of ELX-02. 3) Amended the study objective/endpoints to include the combined therapy in Treatment period 5. 4) Additional changes to provide clarity, correct errors, and additional detail for certain sections were also made in order to increase the understanding of the protocol.
15 July 2021	Amendment 5.0: 1) Included subjects with CF who have phenotypically similar disease to G542X mutations. 2) Addition of a 1-week monotherapy run-in period for Treatment Period 5. 3) One week of monotherapy run-in allowed the generation of contemporaneous monotherapy and combination therapy data making the interpretation of pharmacodynamic effect of ELX-02 more robust. 4) Made Treatment Periods 1 to 4 (TP1 to TP4) optional.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported