



Clinical trial results:

Zephyrus II: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Pamrevlumab in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Summary

EudraCT number	2020-000697-22
Trial protocol	FR HU NL ES CZ DE DK IE PL IT
Global end of trial date	04 September 2023

Results information

Result version number	v2 (current)
This version publication date	25 August 2024
First version publication date	27 July 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	FGCL-3019-095
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04419558
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FibroGen, Inc.
Sponsor organisation address	409 Illinois Street, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, FibroGen, Inc., zephyrus@fibrogen.com
Scientific contact	Clinical Trial Information Desk, FibroGen, Inc., zephyrus@fibrogen.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	04 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2023
Global end of trial reached?	Yes
Global end of trial date	04 September 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the efficacy and safety of Pamrevlumab infusion (30 milligrams [mg]/kilogram [kg] intravenous [IV]) as compared to placebo in participants with Idiopathic Pulmonary Fibrosis (IPF).

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Georgia: 6
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Korea, Republic of: 77
Country: Number of subjects enrolled	Lebanon: 16
Country: Number of subjects enrolled	Mexico: 24
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Peru: 38
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Spain: 17

Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	372
EEA total number of subjects	112

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)	87
From 65 to 84 years	281
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included a Double-blind (DB) Period and an Open-label Extension (OLE) Period.

Period 1

Period 1 title	DB Period (48 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pamrevlumab
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Arm description:

Participants received pamrevlumab 30 mg/kg, administered by IV infusion, every 3 weeks, for a total of up to 17 infusions over 48 weeks in the DB period.

Arm type	Experimental
Investigational medicinal product name	Pamrevlumab
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pamrevlumab was administered per dose and schedule specified in the arm description.

Arm title	Placebo
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Arm description:

Participants received pamrevlumab-matching placebo, administered by IV infusion every 3 weeks for a total of up to 17 infusions over 48 weeks in the DB period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pamrevlumab-matching placebo was administered per schedule specified in the arm description.

Number of subjects in period 1	Pamrevlumab	Placebo
Started	184	188
Received at least 1 dose of study drug	183	188
Completed	47	56
Not completed	137	132
Adverse event, serious fatal	14	11
Participant Decision	4	3
Consent withdrawn by subject	11	7
Lung Transplant	1	-
Adverse event, non-fatal	6	6
Study terminated by sponsor	99	101
Investigator Decision	-	1
Lost to follow-up	1	3
Disease Progression	1	-

Period 2

Period 2 title	OLE Period (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pamrevlumab/Pamrevlumab

Arm description:

Participants who completed the treatment in DB period and entered in the OLE period, continued to receive pamrevlumab 30 mg/kg administered by IV infusion, every 3 weeks for up to 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Pamrevlumab
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pamrevlumab was administered per dose and schedule specified in the arm description.

Arm title	Placebo/Pamrevlumab
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Arm description:

Participants who completed the treatment in DB period and entered in the OLE period, received pamrevlumab 30 mg/kg administered by IV infusion, every 3 weeks for up to 48 weeks.

Arm type	Experimental
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Investigational medicinal product name	Pamrevlumab
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Pamrevlumab was administered per dose and schedule specified in the arm description.

Number of subjects in period 2^[1]	Pamrevlumab/Pamrevlumab	Placebo/Pamrevlumab
Started	41	45
Completed	0	0
Not completed	41	45
Adverse event, serious fatal	4	6
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	1
Study terminated by sponsor	34	37

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All participants who completed DB Period did not enter into the OLE Period.

Baseline characteristics

Reporting groups

Reporting group title	Pamrevlumab
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Reporting group description:

Participants received pamrevlumab 30 mg/kg, administered by IV infusion, every 3 weeks, for a total of up to 17 infusions over 48 weeks in the DB period.

Reporting group title	Placebo
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Reporting group description:

Participants received pamrevlumab-matching placebo, administered by IV infusion every 3 weeks for a total of up to 17 infusions over 48 weeks in the DB period.

Reporting group values	Pamrevlumab	Placebo	Total
Number of subjects	184	188	372
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	70.2 ± 7.8	70.1 ± 8.2	-
Sex: Female, Male Units: participants			
Female	45	44	89
Male	139	144	283
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	42	55	97
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	111	114	225
More than one race	0	0	0
Unknown or Not Reported	29	16	45
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	52	45	97
Not Hispanic or Latino	125	141	266
Unknown or Not Reported	7	2	9
Forced Vital Capacity (FVC)			
FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC was the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters.			
Units: liters arithmetic mean standard deviation	2.4811 ± 0.6477	2.5097 ± 0.6573	-

End points

End points reporting groups

Reporting group title	Pamrevlumab
Reporting group description: Participants received pamrevlumab 30 mg/kg, administered by IV infusion, every 3 weeks, for a total of up to 17 infusions over 48 weeks in the DB period.	
Reporting group title	Placebo
Reporting group description: Participants received pamrevlumab-matching placebo, administered by IV infusion every 3 weeks for a total of up to 17 infusions over 48 weeks in the DB period.	
Reporting group title	Pamrevlumab/Pamrevlumab
Reporting group description: Participants who completed the treatment in DB period and entered in the OLE period, continued to receive pamrevlumab 30 mg/kg administered by IV infusion, every 3 weeks for up to 48 weeks.	
Reporting group title	Placebo/Pamrevlumab
Reporting group description: Participants who completed the treatment in DB period and entered in the OLE period, received pamrevlumab 30 mg/kg administered by IV infusion, every 3 weeks for up to 48 weeks.	

Primary: DB Period: Change From Baseline in FVC at Week 48

End point title	DB Period: Change From Baseline in FVC at Week 48
End point description: FVC is a standard pulmonary function test used to quantify respiratory muscle weakness. FVC was the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Least square (LS) mean and standard error (SE) were analyzed using mixed model repeated measures (MMRM). The ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline, Week 48	

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	76		
Units: liters				
least squares mean (standard error)	-0.30 (\pm 0.057)	-0.33 (\pm 0.059)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Pamrevlumab v Placebo

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6579
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.077

Secondary: DB Period: Change from Baseline in Quantitative Lung Fibrosis (QLF) Volume at Week 48

End point title	DB Period: Change from Baseline in Quantitative Lung Fibrosis (QLF) Volume at Week 48
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End point description:

The QLF volume is calculated as QLF=total lung capacity volume (TLC) * % of quantitative lung fibrosis for fibrosis of the whole lung. LS mean and SE were analyzed using MMRM. The ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 48

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	76		
Units: milliliters				
least squares mean (standard error)	255.14 (± 72.028)	269.15 (± 60.898)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Time to Disease Progression

End point title	DB Period: Time to Disease Progression
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End point description:

Time to disease progression was defined as time from randomization to either the first occurrence of an absolute FVC percent predicted (FVCpp) decline of ≥10% from baseline or death, whichever occurred first. 'Median Time to Event' is an estimated value, which was calculated based on Kaplan-Meier method. For an endpoint in which less than half of the participants have encountered the events, the 'Median

Time to Event' might be longer than the reported timeframe of 48 weeks. The ITT population included all randomized participants. Here, '9.99' and '99999' represents 'NA' that is; 'Data could not be calculated due to smaller number of participants with an event'.

End point type	Secondary
End point timeframe:	
Up to Week 48	

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: weeks				
median (confidence interval 95%)	59.0 (9.99 to 99999)	99999 (49.4 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Time to First Occurrence of Any Component of the Clinical Composite Endpoint, Whichever Occurred First

End point title	DB Period: Time to First Occurrence of Any Component of the Clinical Composite Endpoint, Whichever Occurred First
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End point description:

The components of the clinical composite endpoints included acute idiopathic pulmonary fibrosis (IPF) exacerbation, respiratory hospitalization, or death. 'Median Time to Event' is an estimated value, which was calculated based on Kaplan-Meier method. For an endpoint in which less than half of the participants have encountered the events, the 'Median Time to Event' might be longer than the reported timeframe of 48 weeks. The ITT population included all randomized participants. Here, '99999' represents 'NA' that is; 'Data could not be calculated due to smaller number of participants with an event'.

End point type	Secondary
End point timeframe:	
Up to Week 48	

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: weeks				
median (confidence interval 95%)	99999 (59.0 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Time to First Acute IPF Exacerbation

End point title DB Period: Time to First Acute IPF Exacerbation

End point description:

'Median Time to Event' is an estimated value, which was calculated based on Kaplan-Meier method. For an endpoint in which less than half of the participants have encountered the events, the 'Median Time to Event' might be longer than the reported timeframe of 48 weeks. The ITT population included all randomized participants. Here, '99999' represents 'NA' that is; 'Data could not be calculated due to smaller number of participants with an event'.

End point type Secondary

End point timeframe:

Up to Week 48

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Time to All-Cause Mortality

End point title DB Period: Time to All-Cause Mortality

End point description:

'Median Time to Event' is an estimated value, which was calculated based on Kaplan-Meier method. For an endpoint in which less than half of the participants have encountered the events, the 'Median Time to Event' might be longer than the reported timeframe of 48 weeks. The ITT population included all randomized participants. Here, '9.99' and '99999' represents 'NA' that is; 'Data could not be calculated due to smaller number of participants with an event'.

End point type Secondary

End point timeframe:

Up to Week 48

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: weeks				
median (confidence interval 95%)	99999 (59.0 to 99999)	62.9 (9.99 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DB Period: Time to First Respiratory Hospitalization

End point title DB Period: Time to First Respiratory Hospitalization

End point description:

'Median Time to Event' is an estimated value, which was calculated based on Kaplan-Meier method. For an endpoint in which less than half of the participants have encountered the events, the 'Median Time to Event' might be longer than the reported timeframe of 48 weeks. The ITT population included all randomized participants. Here, '99999' represents 'NA' that is; 'Data could not be calculated due to smaller number of participants with an event'.

End point type Secondary

End point timeframe:

Up to Week 48

End point values	Pamrevlumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	188		
Units: weeks				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 104

Adverse event reporting additional description:

As pre-specified, All-cause mortality data were collected and reported for all enrolled participants; and Serious and Non-serious adverse events data were collected and reported for all participants who received any dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	DB Period: Pamrevlumab
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Reporting group description:

Participants received pamrevlumab 30 mg/kg, administered by IV infusion, every 3 weeks, for a total of up to 17 infusions over 48 weeks in the DB period.

Reporting group title	OLE Period: Pamrevlumab
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Reporting group description:

Participants who completed the treatment in DB period and entered in the OLE period, received pamrevlumab 30 mg/kg administered by IV infusion, every 3 weeks for up to 48 weeks.

Reporting group title	DB Period: Placebo
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Reporting group description:

Participants received pamrevlumab-matching placebo, administered by IV infusion every 3 weeks for a total of up to 17 infusions over 48 weeks in the DB period.

Serious adverse events	DB Period: Pamrevlumab	OLE Period: Pamrevlumab	DB Period: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 183 (20.77%)	20 / 86 (23.26%)	37 / 188 (19.68%)
number of deaths (all causes)	16	12	15
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Metastases to liver			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Small cell lung cancer			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery aneurysm			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Non-cardiac chest pain			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Asthenia			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	9 / 183 (4.92%)	12 / 86 (13.95%)	10 / 188 (5.32%)
occurrences causally related to treatment / all	4 / 9	1 / 12	1 / 10
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 183 (0.55%)	1 / 86 (1.16%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	1 / 183 (0.55%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	2 / 188 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
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 failure			
subjects affected / exposed	4 / 183 (2.19%)	2 / 86 (2.33%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 183 (1.64%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	3 / 183 (1.64%)	2 / 86 (2.33%)	2 / 188 (1.06%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin injury			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thoracic vertebral fracture subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Myocardial infarction subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicobrachial syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Vertebrobasilar stroke			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Syncope			

subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	2 / 188 (1.06%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Eye disorders			
Scleritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Hepatic cirrhosis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Acute kidney injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Empyema			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 183 (1.09%)	0 / 86 (0.00%)	0 / 188 (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
Nasal abscess			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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

Pneumonia			
subjects affected / exposed	9 / 183 (4.92%)	0 / 86 (0.00%)	10 / 188 (5.32%)
occurrences causally related to treatment / all	3 / 9	0 / 0	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 86 (1.16%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Respiratory tract infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 86 (1.16%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 86 (0.00%)	0 / 188 (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
Urinary tract infection			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 183 (0.00%)	0 / 86 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	DB Period: Pamrevlumab	OLE Period: Pamrevlumab	DB Period: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 183 (45.36%)	21 / 86 (24.42%)	74 / 188 (39.36%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 183 (6.01%)	4 / 86 (4.65%)	7 / 188 (3.72%)
occurrences (all)	14	4	8
Fatigue			
subjects affected / exposed	11 / 183 (6.01%)	0 / 86 (0.00%)	5 / 188 (2.66%)
occurrences (all)	15	0	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	14 / 183 (7.65%)	4 / 86 (4.65%)	15 / 188 (7.98%)
occurrences (all)	22	5	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 183 (14.21%)	5 / 86 (5.81%)	24 / 188 (12.77%)
occurrences (all)	38	6	27
Dyspnoea			
subjects affected / exposed	16 / 183 (8.74%)	5 / 86 (5.81%)	12 / 188 (6.38%)
occurrences (all)	18	7	16
Infections and infestations			
COVID-19			
subjects affected / exposed	20 / 183 (10.93%)	8 / 86 (9.30%)	16 / 188 (8.51%)
occurrences (all)	21	8	16
Nasopharyngitis			
subjects affected / exposed	13 / 183 (7.10%)	4 / 86 (4.65%)	14 / 188 (7.45%)
occurrences (all)	15	5	15
Bronchitis			
subjects affected / exposed	9 / 183 (4.92%)	0 / 86 (0.00%)	12 / 188 (6.38%)
occurrences (all)	10	0	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2021	<p>It included following changes: - Timeframe for efficacy assessments of secondary study endpoints were updated from Week 52 to Week 48. - Clarification was added that for calculation of Global Alignment and Proportion (GAP) Score, the Best-Test Review (BTR) assessment provided by the spirometry vendor Over-Reader of the screening value is to be used. - A final safety follow-up phone call 60 day post last dose was added. - Participant eligibility criteria updated:</p> <ul style="list-style-type: none">o Updated Inclusion criterion to add clarity about requirements of a High-resolution computed tomography (HRCT) scan done within 3 months of screening, to meet screening scan requirements.o Updated FVCpp eligibility criteria to be more inclusive, without compromising the target participant population.o Updated diffusing capacity of the lungs for carbon monoxide (DLCO) eligibility criteria and window to be more inclusive, without compromising the target participant population.o Revised per Clinical Trial Facilitation Group (CTFG) recommendation.o To ensure exclusion of participants who may have a history of allergic or anaphylactic reaction to any component of the excipient.o New criteria added to provide more specific guidance for the exclusionary intercurrent conditions and medications/vaccines. <p>- Clarified to ensure that Investigators may unblind single participant in emergency situations without the need for Sponsor approval. - Clarified that if a participant has a life-threatening infusion-associated AE, study drug treatment must be permanently discontinued. - Added guidance on recommended timing between COVID-19 vaccination and study drug administration. - Incorporated Guidance from the Food and Drug Administration (FDA)/European Medicines Agency (EMA) in response to the COVID-19 pandemic and resulting need for flexibility with respect to study assessments and visit schedule. - Added on-study Physical Exams (PEs) and electrocardiograms (ECGs).</p>
09 January 2023	<p>It included following changes: - The primary efficacy endpoint was updated from time to disease progression to change in FVC. - The secondary endpoints were updated to reflect shift in the primary efficacy endpoint and several secondary endpoints were also moved to exploratory endpoints; additionally, a composite efficacy endpoint was added. - The exploratory endpoints were updated to include several of the previous secondary endpoints.</p> <p>- Clarified required procedures/assessments at early termination visits. - Added language describing infusion duration and post-infusion observation periods in the OLE. - Clarified requirements for medications and supplies for home health care. - Added preliminary non-clinical study results. - Added language regarding pregnancy testing. - Added pharmacokinetic (PK), Human Anti-Human Antibody (HAHA), HAHA-NA, Connective Tissue Growth Factor, and tryptase scheduled blood draws at the time of any suspected hypersensitivity/anaphylactic reactions. - Added additional time-points as follows in the main period of the study: CTGF at Weeks 24 and 36, and HAHA and HAHA-NA at Week 36 and Week 48/last dose/early termination (ET). - Clarified the order of Patient-Reported Outcome questionnaire administration. - Added objectives in the OLE period. - Added additional safety assessments – vitals and immunogenicity. - Clarified main period procedures and AEs. - Added OLE home health care requirements.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported