



Clinical trial results:

A Randomised, Double-Blind, Placebo-Controlled Multicentre Clinical Trial of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis Patients.

Summary

EudraCT number	2015-003878-33
Trial protocol	GB DK NL DE GR ES IT PT
Global end of trial date	27 September 2019

Results information

Result version number	v1
This version publication date	18 February 2021
First version publication date	18 February 2021

Trial information

Trial identification

Sponsor protocol code	MOL-PAP-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02702180
WHO universal trial number (UTN)	-
Other trial identifiers	IMPALA: IMPALA

Notes:

Sponsors

Sponsor organisation name	Savara ApS
Sponsor organisation address	Slotsmarken 17, 1.th., Hørsholm, Denmark, DK-2970
Public contact	Cecilia Ganslandt, Savara ApS, +45 79301414, info@savarapharma.com
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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	08 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2019
Global end of trial reached?	Yes
Global end of trial date	27 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare efficacy of inhaled molgramostim on the Alveolar-arterial oxygen difference ((A-a)DO₂) with placebo after 24-weeks treatment.

Protection of trial subjects:

Subjects could be discontinued from treatment and assessments at any time, if deemed necessary by the investigator.

Potential reasons for discontinuation of treatment included lack of efficacy/worsening of disease and unacceptable AE.

WLL was applied as rescue therapy. The criterion for performing WLL was clinical worsening of aPAP based on symptoms, reduced exercise capacity and/or findings of hypoxemia or desaturation according to the investigator's judgement.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2016
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	Switzerland: 1
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Greece: 4

Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	138
EEA total number of subjects	61

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)	113
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Key incl. criteria: aPAP (diagnosed by CT/biopsy/BAL, and increased GM-CSF autoantibodies); confirmed stable/progressive for ≥ 2 months prior to Baseline; (A-a)DO₂ ≥ 25 mmHg; PaO₂ < 75 mmHg at rest/desaturation > 4 % points in 6MWT.

235 were screened. 138 entered the DB period. Most Scr. failures were related to key incl. criteria listed above.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MOL-OD

Arm description:

Molgramostim 300 µg nebuliser solution administered once-daily; referred to as MOL-OD.

Arm type	Experimental
Investigational medicinal product name	Molgramostim nebuliser solution 300 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Molgramostim nebuliser solution 300 µg, administered once-daily by inhalation using an investigational eFlow® Nebuliser System.

Arm title	MOL-INT
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Arm description:

Molgramostim 300 µg nebuliser solution and matching placebo administered intermittently (12 cycles of 7 days molgramostim nebuliser solution, 7 days placebo; both administered once-daily); referred to as MOL-INT.

Arm type	Experimental
Investigational medicinal product name	Molgramostim nebuliser solution 300 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Molgramostim nebuliser solution 300 µg, administered once-daily every other week by inhalation using an investigational eFlow® Nebuliser System.

Investigational medicinal product name	Placebo nebuliser solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo nebuliser solution administered once-daily every other week by inhalation using an investigational eFlow® Nebuliser System.

Arm title	Placebo
Arm description: Placebo nebuliser solution administered once-daily.	
Arm type	Placebo
Investigational medicinal product name	Placebo nebuliser solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo nebuliser solution administered once-daily by inhalation using an investigational eFlow® Nebuliser System.

Number of subjects in period 1	MOL-OD	MOL-INT	Placebo
Started	46	45	47
Completed	45	44	43
Not completed	1	1	4
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	-	-	1
Lack of efficacy	-	-	1
Protocol deviation	-	-	2

Baseline characteristics

Reporting groups

Reporting group title	MOL-OD
Reporting group description: Molgramostim 300 µg nebuliser solution administered once-daily; referred to as MOL-OD.	
Reporting group title	MOL-INT
Reporting group description: Molgramostim 300 µg nebuliser solution and matching placebo administered intermittently (12 cycles of 7 days molgramostim nebuliser solution, 7 days placebo; both administered once-daily); referred to as MOL-INT.	
Reporting group title	Placebo
Reporting group description: Placebo nebuliser solution administered once-daily.	

Reporting group values	MOL-OD	MOL-INT	Placebo
Number of subjects	46	45	47
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	38	41
From 65-84 years	12	7	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.0	49.2	46.1
standard deviation	± 13.32	± 14.06	± 14.84
Gender categorical Units: Subjects			
Female	18	19	22
Male	28	26	25

Reporting group values	Total		
Number of subjects	138		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	113		
From 65-84 years	25		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	59		
Male	79		

End points

End points reporting groups

Reporting group title	MOL-OD
Reporting group description: Molgramostim 300 µg nebuliser solution administered once-daily; referred to as MOL-OD.	
Reporting group title	MOL-INT
Reporting group description: Molgramostim 300 µg nebuliser solution and matching placebo administered intermittently (12 cycles of 7 days molgramostim nebuliser solution, 7 days placebo; both administered once-daily); referred to as MOL-INT.	
Reporting group title	Placebo
Reporting group description: Placebo nebuliser solution administered once-daily.	

Primary: Absolute change from baseline of (A-a)DO₂

End point title	Absolute change from baseline of (A-a)DO ₂
End point description: Absolute change from baseline of (A-a)DO ₂ after 24 weeks of treatment.	
End point type	Primary
End point timeframe: Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	43	43	
Units: mmHg				
arithmetic mean (standard deviation)	-12.1 (± 14.58)	-11.7 (± 17.06)	-8.8 (± 16.14)	

Statistical analyses

Statistical analysis title	Analysis of primary endpoint (FAS)
Comparison groups	MOL-OD v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1688
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	-4.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	2

Statistical analysis title	Analysis of primary endpoint (FAS)
Comparison groups	MOL-INT v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3968
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	3.7

Secondary: Change from baseline in 6 minute walking distance (6MWD)	
End point title	Change from baseline in 6 minute walking distance (6MWD)
End point description:	
Change from baseline in 6MWD after 24 weeks of treatment. This was a Key Secondary Endpoint.	
End point type	Secondary
End point timeframe:	
Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	43	
Units: meters				
arithmetic mean (standard deviation)	39.6 (± 95.89)	11.3 (± 81.94)	6.0 (± 110.46)	

Statistical analyses	
Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-OD v Placebo

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3159 ^[1]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	20.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	61

Notes:

[1] - Not adjusted for multiplicity.

Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-INT v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7809 ^[2]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.1
upper limit	45.2

Notes:

[2] - Not adjusted for multiplicity.

Secondary: Change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score

End point title	Change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score
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End point description:

Change from baseline in SGRQ total score after 24 weeks of treatment.

SGRQ scores (total and components) range from 0 to 100, with higher scores indicating more limitations.

This was a Key Secondary Endpoint.

End point type	Secondary
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End point timeframe:

Baseline to week 24.

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	44	43	
Units: Score				
arithmetic mean (standard deviation)	-12.3 (\pm 14.30)	-12.0 (\pm 15.12)	-4.7 (\pm 12.83)	

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-OD v Placebo
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0103 ^[3]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	-1.8

Notes:

[3] - Not adjusted for multiplicity.

Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-INT v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0173 ^[4]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	-1.3

Notes:

[4] - Not adjusted for multiplicity.

Secondary: Time to WLL during 24 weeks of treatment

End point title	Time to WLL during 24 weeks of treatment
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End point description:

Time to need for WLL during 24 weeks of treatment.

This was a Key Secondary Endpoint.

The median time to WLL could not be estimated due to the small number of events.

End point type	Secondary
End point timeframe:	
Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of subjects in need of WLL	4	4	6	

Statistical analyses

Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-OD v Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4934 ^[5]
Method	Logrank

Notes:

[5] - Not adjusted for multiplicity.

Statistical analysis title	Analysis of key secondary endpoint (FAS)
Comparison groups	MOL-INT v Placebo
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4787 ^[6]
Method	Logrank

Notes:

[6] - Not adjusted for multiplicity.

Secondary: Change from baseline in DLCO (% predicted)

End point title	Change from baseline in DLCO (% predicted)
End point description:	
Absolute change from baseline in DLCO (% predicted) after 24 weeks of treatment. Hemoglobin-adjusted values were used. This was a Further Secondary Endpoint.	
End point type	Secondary
End point timeframe:	
Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	42	
Units: % predicted				
arithmetic mean (standard deviation)	11.6 (\pm 17.30)	7.7 (\pm 11.41)	3.9 (\pm 10.86)	

Statistical analyses

Statistical analysis title	Analysis of further secondary endpoint (FAS)
Comparison groups	MOL-OD v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0074 ^[7]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	13.6

Notes:

[7] - No adjustment for multiplicity.

Statistical analysis title	Analysis of further secondary endpoint (FAS)
Comparison groups	MOL-INT v Placebo
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3097 ^[8]
Method	ANCOVA
Parameter estimate	LSmean difference
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	8.7

Notes:

[8] - No adjustment for multiplicity.

Secondary: Number of serious adverse events (SAEs)

End point title	Number of serious adverse events (SAEs)
End point description:	
Number of SAEs reported during 24 weeks of treatment	
End point type	Secondary

End point timeframe:

Baseline to week 24.

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of events	13	5	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse drug reactions (ADRs)

End point title	Number of adverse drug reactions (ADRs)
End point description: Number of ADRs (AEs with relation to IP = probable or possible) reported during 24 weeks of treatment.	
End point type	Secondary
End point timeframe: Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of events	53	27	33	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe adverse events

End point title	Number of severe adverse events
End point description: Number of severe AEs reported during 24 weeks of treatment.	
End point type	Secondary
End point timeframe: Baseline to week 24.	

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of events	28	11	38	

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events leading to treatment discontinuation

End point title	Adverse events leading to treatment discontinuation
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End point description:

Number of subjects with one or more AEs leading to treatment discontinuation during 24 weeks of treatment.

End point type	Secondary
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End point timeframe:

Baseline to week 24.

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of subjects with events	2	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events

End point title	Number of adverse events
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to week 24.

End point values	MOL-OD	MOL-INT	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	45	47	
Units: Number of events	215	191	192	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 24.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	MOL-OD
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Reporting group description:

Molgramostim 300 µg nebuliser solution administered once-daily (referred to as MOL-OD)

Reporting group title	MOL-INT
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Reporting group description:

Molgramostim 300 µg nebuliser solution and matching placebo administered intermittently (12 cycles of 7 days molgramostim nebuliser solution, 7 days placebo; both administered once daily); referred to as MOL-INT.

Reporting group title	Placebo
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Reporting group description:

Placebo nebuliser solution administered once-daily.

Serious adverse events	MOL-OD	MOL-INT	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 46 (17.39%)	5 / 45 (11.11%)	8 / 47 (17.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Drug detoxification			
subjects affected / exposed	0 / 46 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (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
Epilepsy			

subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (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			
Alveolar proteinosis			
subjects affected / exposed	3 / 46 (6.52%)	3 / 45 (6.67%)	6 / 47 (12.77%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 46 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (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
Dyspnoea			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (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 failure			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Gambling disorder			
subjects affected / exposed	0 / 46 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 46 (2.17%)	1 / 45 (2.22%)	0 / 47 (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
Diverticulitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 45 (2.22%)	0 / 47 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 45 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 45 (0.00%)	0 / 47 (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

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	MOL-OD	MOL-INT	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 46 (84.78%)	41 / 45 (91.11%)	40 / 47 (85.11%)
Investigations			
Weight increased			
subjects affected / exposed	3 / 46 (6.52%)	5 / 45 (11.11%)	0 / 47 (0.00%)
occurrences (all)	4	6	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 46 (13.04%)	7 / 45 (15.56%)	7 / 47 (14.89%)
occurrences (all)	9	9	16

Dizziness subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2	2 / 45 (4.44%) 2	2 / 47 (4.26%) 4
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	10 / 46 (21.74%) 11 2 / 46 (4.35%) 2	2 / 45 (4.44%) 2 3 / 45 (6.67%) 3	1 / 47 (2.13%) 2 3 / 47 (6.38%) 4
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	6 / 45 (13.33%) 6	3 / 47 (6.38%) 3
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Alveolar proteinosis subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	15 / 46 (32.61%) 22 5 / 46 (10.87%) 8 3 / 46 (6.52%) 4 4 / 46 (8.70%) 5	12 / 45 (26.67%) 18 7 / 45 (15.56%) 7 5 / 45 (11.11%) 5 3 / 45 (6.67%) 3	11 / 47 (23.40%) 12 4 / 47 (8.51%) 5 8 / 47 (17.02%) 18 3 / 47 (6.38%) 3
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 5 2 / 46 (4.35%) 2	3 / 45 (6.67%) 4 0 / 45 (0.00%) 0	1 / 47 (2.13%) 1 4 / 47 (8.51%) 4
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 46 (15.22%) 10	10 / 45 (22.22%) 12	6 / 47 (12.77%) 6
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2	2 / 45 (4.44%) 2	2 / 47 (4.26%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0	3 / 45 (6.67%) 3	3 / 47 (6.38%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2016	Additions reflecting 1) the implementation of a data safety monitoring board and 2) new data from long-term toxicity study.
11 October 2016	Exclusion criteria regarding immunosuppressive treatment updated to only include treatment causing significant immunosuppression. Exclusion criterion regarding liver impairment changed to from 3 to 4 times the upper limit of aspartate aminotransferase and alanine aminotransferase. Open-label FU treatment changed from only to be given in case of worsening of (A-a)DO ₂ of more than 10 mmHg from baseline, to be given according to investigator's discretion and if so, dosed intermittently 7-days on / 7-days off treatment for 24 weeks, thereafter dosing according to investigator's judgement. Criterion for rescue treatment revised to comprise an overall evaluation of treatment requirement by the investigator, including symptoms reported by the patient, rather than only in case of worsening of (A-a)DO ₂ of more than 10 mmHg from baseline. Analysis for antibodies against the excipients polyethylene glycol and recombinant human albumin were added.
06 June 2017	Sample size increased to 90 randomized. Updates to key efficacy objectives/endpoints (3 key secondary: 6MWT, SGRQ, WLL). Key secondary objective for safety added. FU for subjects included after this amendment is 24 weeks. FU for subjects included before is 48 weeks. Molgramostim treatment in the FU period applied for all subjects. Additional efficacy assessments (dyspnea, cough, quality of life) and safety laboratory assessments added in the FU period. Possibility to conduct WLL in the screening period removed. Exclusion criterion re. time since last WLL reduced to 1 month, criteria re. liver/renal impairment removed. Statistical methods updated (e.g., to account for multiplicity of key secondary endpoints). Assessment of anti-drug-antibodies added at week 4.
01 December 2017	Plan for blinded sample size re-estimation added. Statistical methodology for the primary analyses aligned across regions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32897035>