Clinical trial results:
Phase-Ib/IIa study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of orally inhaled multiple doses of POL6014 (lonodelestat) in patients with Cystic Fibrosis

Summary

EudraCT number	2018-002550-71
Trial protocol	DE
Global end of trial date	30 December 2020

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	SNT-I-018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03748199
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santhera Pharmaceuticals (Switzerland) Ltd
Sponsor organisation address	Hohenrainstrasse 24, Pratteln, Switzerland, 4133
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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	13 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2020
Global end of trial reached?	Yes
Global end of trial date	30 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To assess the safety and tolerability of up to three multiple ascending dose levels of inhaled POL6014 after 15 days q.d. or b.i.d.
-To identify the highest tolerated dose level and associated dose regimen of inhaled POL6014 after 15 days q.d. or b.i.d. treatment.

Protection of trial subjects:

This study was completed and archived according to the guidelines of Good Clinical Practice (GCP), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 (CPMP/ICH/135/95) and conducted in compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2018
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	Germany: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 37 patients were enrolled for screening. Of these patients, 33 were randomized whereas 4 patients were screening failures.

Pre-assignment

Screening details:

Overall, 37 patients were enrolled for screening. Of these patients, 33 were randomized whereas 4 patients were screening failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1A-(80 mg/day)

Arm description:

80 mg QD lonodelestat or matching placebo for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)

Arm type	Experimental
Investigational medicinal product name	lonodelestat
Investigational medicinal product code	
Other name	POL6014
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

80 mg QD lonodelestat or matching placebo for 15 days, Inhalation use

Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

lonodelestat matching Placebo, Inhalation use

Arm title	Cohort 2A (160mg/day)

Arm description:

Cohort 2A - 160mg lonodelestat or matching Placebo QD for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)

Arm type	Experimental

Investigational medicinal product name	lonodelestat
Investigational medicinal product code	
Other name	POL6014
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

160 mg QD lonodelestat or matching placebo for 15 days, Inhalation use

Arm title	Cohort 2B (160mg/day)

Arm description:

Cohort 2B - 80mg lonodelestat or matching Placebo BID for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)

Arm type	Experimental
Investigational medicinal product name	lonodelestat
Investigational medicinal product code	
Other name	POL6014
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

80 mg BID lonodelestat or matching placebo for 15 days, Inhalation use

Arm title	Cohort C

Arm description:

Cohort C - 40mg lonodelestat or matching Placebo QD for 28 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)

Arm type	Experimental
Investigational medicinal product name	lonodelestat
Investigational medicinal product code	
Other name	POL6014
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

40 mg QD lonodelestat or matching placebo for 28 days, Inhalation use

Number of subjects in period 1	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)
Started	6	8	6
Completed	6	8	6
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Cohort 2B (160mg/day)	Cohort C
Started	6	6
Completed	5	6
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

Overall, 37 patients were enrolled for screening. Of these patients, 33 were randomized whereas 4 patients were screening failures. 31 patients completed the study according to the protocol. One patient was randomized to the placebo QD group of Cohort C but was not treated due to withdrawal of consent. Another patient randomized to 80 mg lonodelestat BID terminated the study prematurely due to withdrawal of consent.

Reporting group values	Overall trial	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	32		
standard deviation	± 9.7	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	28	28	

End points

End points reporting groups

Reporting group title	Cohort 1A-(80 mg/day)
Reporting group description:	
80 mg QD lonodelestat or matching placebo for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Cohort 2A (160mg/day)
Reporting group description:	
Cohort 2A - 160mg lonodelestat or matching Placebo QD for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)	
Reporting group title	Cohort 2B (160mg/day)
Reporting group description:	
Cohort 2B - 80mg lonodelestat or matching Placebo BID for 15 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)	
Reporting group title	Cohort C
Reporting group description:	
Cohort C - 40mg lonodelestat or matching Placebo QD for 28 days,8 patients per cohort (6 patients on verum, 2 patients on placebo)	

Primary: 6-Proportion of patients with local irritation of the nose or pharynx by visual inspection

End point title	6-Proportion of patients with local irritation of the nose or pharynx by visual inspection[1]
End point description:	
Local irritation of the nose or pharynx by visual inspection and symptomatology	
End point type	Primary
End point timeframe:	
TEAEs were defined as AEs that started or worsened after the 1st dose of the IMP until the follow-up visit.	

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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subjects				
Patients with event	1	0	1	1
Respiratory, thoracic and mediastinal disorders	1	0	1	1
Epistaxis	0	0	1	0
Oropharyngeal pain	1	0	0	0
Rhinorrhoea	0	0	1	1

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Patients with event	0			
Respiratory, thoracic and mediastinal disorders	0			
Epistaxis	0			
Oropharyngeal pain	0			
Rhinorrhoea	0			

Statistical analyses

No statistical analyses for this end point

Primary: 7-Proportion of patients with bronchospasm by symptoms such as dyspnoea, wheezing, chest tightness, cough

End point title	7-Proportion of patients with bronchospasm by symptoms such as dyspnoea, wheezing, chest tightness, cough[2]

End point description:

Bronchospasm by symptoms such as dyspnea, wheezing, chest tightness, and/or cough

End point type	Primary

End point timeframe:

TEAEs were defined as AEs that started or worsened after the 1st dose of the IMP until the follow-up visit.

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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	6	6
Units: Patients				
Patients with any event	1	1	3	6
General disorders and administration site conditio	1	0	1	3
Chest discomfort	1	0	1	3
Investigations	0	0	0	1
Forced expiratory volume decreased	0	0	0	1
Respiratory, thoracic and mediastinal disorders	1	1	3	6
Bronchospasm	0	0	1	0
Chest discomfort.	0	0	0	1

Cough	1	0	2	1
Dyspnoea	1	0	1	4
Obstructive airways disorder	0	0	0	3
Oropharyngeal pain	0	0	0	1
Productive cough	0	1	0	0
Wheezing	1	0	0	1

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Patients				
Patients with any event	2			
General disorders and administration site conditio	0			
Chest discomfort	0			
Investigations	0			
Forced expiratory volume decreased	0			
Respiratory, thoracic and mediastinal disorders	2			
Bronchospasm	0			
Chest discomfort.	0			
Cough	0			
Dyspnoea	1			
Obstructive airways disorder	0			
Oropharyngeal pain	1			
Productive cough	0			
Wheezing	0			

Statistical analyses

No statistical analyses for this end point

Primary: 9-Changes from baseline in oxygen saturation in peripheral blood as measured by pulse

End point title	9-Changes from baseline in oxygen saturation in peripheral blood as measured by pulse[3]

End point description:

End point type	Primary

End point timeframe:

15 days

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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8[4]	6	6[5]
Units: Oxygen Saturation [%]				
arithmetic mean (standard deviation)				
Change D8 - Baseline	0.5 (± 1.38)	0.5 (± 1.41)	-1.2 (± 2.86)	0.5 (± 2.59)
Change D15 - Baseline	0.8 (± 1.33)	1.0 (± 1.31)	-2.8 (± 1.33)	-2.6 (± 3.29)
Change Follow-up - Baseline	0.5 (± 0.84)	1.2 (± 2.48)	-1.2 (± 2.23)	1.3 (± 1.21)

Notes:

[4] - Change Follow-up - Baseline: N=6

[5] - Change D15 - Baseline: N=5

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Oxygen Saturation [%]				
arithmetic mean (standard deviation)				
Change D8 - Baseline	-1.3 (± 3.78)			
Change D15 - Baseline	0.0 (± 0.89)			
Change Follow-up - Baseline	0.0 (± 0.63)			

Statistical analyses

No statistical analyses for this end point

Primary: 8A-Changes from baseline and pre-dose in lung function parameters by spirometry-FVC

End point title	8A-Changes from baseline and pre-dose in lung function parameters by spirometry-FVC[6]

End point description:

End point type	Primary

End point timeframe:

15 days

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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Percent Predicted FVC according to GLI f				
arithmetic mean (standard deviation)				

Screening	74.294 (± 10.7952)	95.127 (± 23.8408)	85.572 (± 6.0049)	77.191 (± 11.2056)
D1 - 1h post-morning dose	71.836 (± 12.0833)	92.746 (± 24.2705)	79.743 (± 7.2022)	73.967 (± 8.4247)
D8 - pre-morning dose	72.433 (± 12.8110)	96.897 (± 25.0244)	78.357 (± 5.6837)	71.115 (± 12.9275)
D8 - 3h post-morning dose	71.239 (± 11.8307)	95.354 (± 24.0326)	78.548 (± 6.1711)	68.465 (± 14.5707)
D15 - pre-morning dose	69.353 (± 11.9325)	92.459 (± 25.8670)	74.207 (± 8.1306)	68.452 (± 8.9347)
D15 - 3h post-morning dose	68.211 (± 10.1422)	91.685 (± 21.7058)	75.463 (± 8.1343)	67.012 (± 10.5575)
Follow-up	71.670 (± 12.1342)	95.529 (± 27.6120)	84.944 (± 2.4961)	74.611 (± 12.7714)

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percent Predicted FVC according to GLI f				
arithmetic mean (standard deviation)				
Screening	78.216 (± 16.9532)			
D1 - 1h post-morning dose	74.139 (± 18.2907)			
D8 - pre-morning dose	77.999 (± 16.9712)			
D8 - 3h post-morning dose	75.124 (± 18.9872)			
D15 - pre-morning dose	73.607 (± 16.2156)			
D15 - 3h post-morning dose	72.722 (± 17.1640)			
Follow-up	74.337 (± 17.3027)			

Statistical analyses

No statistical analyses for this end point

Primary: 8B-Changes from baseline and pre-dose in lung function parameters by spirometry- FEV1

End point title	8B-Changes from baseline and pre-dose in lung function parameters by spirometry- FEV1[7]
End point description:	
FEV1 [%] - absolute change from baseline	
End point type	Primary
End point timeframe:	
15 days	

Notes:

[7] - 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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	6	6
Units: Percent Predicted FEV1 according to GLI				
arithmetic mean (standard deviation)				
Change D1 - 1h post-morning dose-Baseline	-1.327 (± 2.7409)	2.188 (± 6.3432)	-1.253 (± 2.7017)	-3.643 (± 1.9381)
Change D8 - pre-morning dose - Baseline	-2.150 (± 4.6335)	4.816 (± 6.9112)	-6.343 (± 9.1191)	-8.683 (± 6.1120)
Change D15 - pre-morning dose - Baseline	-7.285 (± 6.6758)	0.852 (± 5.6222)	-11.734 (± 7.9541)	-14.005 (± 9.6930)
Change Follow-up - Baseline	-2.848 (± 7.4268)	6.878 (± 6.6505)	-1.153 (± 7.9842)	-4.979 (± 4.9556)

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Percent Predicted FEV1 according to GLI				
arithmetic mean (standard deviation)				
Change D1 - 1h post-morning dose-Baseline	-1.167 (± 4.1864)			
Change D8 - pre-morning dose - Baseline	3.381 (± 2.5686)			
Change D15 - pre-morning dose - Baseline	-2.901 (± 3.2141)			
Change Follow-up - Baseline	-1.590 (± 3.3609)			

Statistical analyses

No statistical analyses for this end point

Primary: 1-Proportion of patients with abnormal physical examination findings

End point title	1-Proportion of patients with abnormal physical examination findings[8]

End point description:

End point type	Primary

End point timeframe:

trial duration

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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	6	6
Units: Subjects				
Subjects	2	0	2	5

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Subjects				
Subjects	4			

Statistical analyses

No statistical analyses for this end point

Primary: 4-Changes from baseline and pre-dose in ECG parameters

End point title	4-Changes from baseline and pre-dose in ECG parameters[9]
End point description:	
ECG Mean Ventricular Rate [beats/min]	
End point type	Primary
End point timeframe:	
trial duraction	

Notes:

[9] - 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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	6	6
Units: beats/min				
arithmetic mean (standard deviation)				
Change D1 - 4h post-morning dose - Baseline	1.7 (± 12.91)	5.1 (± 8.18)	6.2 (± 7.25)	3.0 (± 7.97)

Change D8 - pre-morning dose - Baseline	2.0 (± 8.60)	0.9 (± 7.85)	1.0 (± 4.20)	3.3 (± 13.50)
Change D8 - 4h post-morning dose - Baseline	0.7 (± 13.26)	0.4 (± 7.41)	9.3 (± 4.59)	1.5 (± 11.26)
Change D15 - pre-morning dose - Baseline	0.7 (± 12.21)	-0.6 (± 5.55)	-2.0 (± 11.63)	12.2 (± 15.94)
Change D15 - 4h post-morning dose - Baseline	5.5 (± 14.79)	0.4 (± 5.29)	7.2 (± 12.56)	9.4 (± 21.07)
Change Follow-up - Baseline	3.3 (± 8.31)	7.5 (± 16.02)	0.3 (± 10.03)	2.7 (± 16.15)

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: beats/min				
arithmetic mean (standard deviation)				
Change D1 - 4h post-morning dose - Baseline	0.8 (± 4.62)			
Change D8 - pre-morning dose - Baseline	-1.3 (± 8.71)			
Change D8 - 4h post-morning dose - Baseline	1.0 (± 4.38)			
Change D15 - pre-morning dose - Baseline	3.7 (± 5.61)			
Change D15 - 4h post-morning dose - Baseline	2.7 (± 6.59)			
Change Follow-up - Baseline	-3.0 (± 8.72)			

Statistical analyses

No statistical analyses for this end point

Primary: 5- Occurrence and severity of AEs

End point title	5- Occurrence and severity of AEs[10]

End point description:

End point type	Primary

End point timeframe:

trial duration

Notes:

[10] - 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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8	6	6
Units: number of adverse events				
Total number of TEAE	19	13	18	36
Number of TEAE possibly related to study drug	2	3	9	16
Number of local TEAE related to inhalation	3	1	2	13
Number of TEAE of severity grade 3, 4 or 5	0	0	0	0
Number of serious TEAE	0	0	0	0
Number of TEAE leading to study drug interruption	0	0	1	2
Number of TEAE leading to study drug discontinuati	0	0	0	2

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: number of adverse events				
Total number of TEAE	19			
Number of TEAE possibly related to study drug	8			
Number of local TEAE related to inhalation	7			
Number of TEAE of severity grade 3, 4 or 5	0			
Number of serious TEAE	0			
Number of TEAE leading to study drug interruption	0			
Number of TEAE leading to study drug discontinuati	0			

Statistical analyses

No statistical analyses for this end point

Primary: 2 Changes from baseline in laboratory safety assessments (clinical chemistry, haematology, urinalysis)

End point title	2 Changes from baseline in laboratory safety assessments (clinical chemistry, haematology, urinalysis)[11]

End point description:

representative for the laboratory parameters collected only the albumin data is presented here,full summary of laboratory parameters is provided in appendix 14.3.5-1 of the CSR

End point type	Primary

End point timeframe:

trial duration

Notes:

[11] - 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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8[12]	6	6[13]
Units: g/dl				
arithmetic mean (standard deviation)				
Change D8 - Baseline	0.12 (± 0.306)	0.03 (± 0.176)	0.10 (± 0.176)	0.17 (± 0.225)
Change D15 - Baseline	-0.12 (± 0.160)	0.03 (± 0.194)	-0.11 (± 0.209)	0.08 (± 0.084)
Change Follow-up - Baseline	0.05 (± 0.187)	0.14 (± 0.093)	0.08 (± 0.223)	0.17 (± 0.082)

Notes:

[12] - subjects change follow up- baseline: 6

[13] - subjects change D15-baseline=5

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: g/dl				
arithmetic mean (standard deviation)				
Change D8 - Baseline	-0.19 (± 0.267)			
Change D15 - Baseline	-0.16 (± 0.245)			
Change Follow-up - Baseline	-0.02 (± 0.318)			

Statistical analyses

No statistical analyses for this end point

Primary: 3 Changes from baseline and pre-dose in vital signs (blood pressure, pulse, respiratory rate body temperature)

End point title	3 Changes from baseline and pre-dose in vital signs (blood pressure, pulse, respiratory rate body temperature)[14]

End point description:

representative for the vital signs parameters collected only the temperature data is presented here,full summary of vital signs parameters is provided in appendix 14.3.6-1 of the CSR

End point type	Primary

End point timeframe:

trial duration

Notes:

[14] - 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: The sample size of each cohort was too small to perform statistical tests on any of the components of the PEP.

Descriptive analysis was conducted for these groups.

End point values	Cohort 1A-(80 mg/day)	Placebo	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	8[15]	6	6[16]
Units: celcius				
arithmetic mean (standard deviation)				
Change D1 - 1h post-morning dose - Baseline	0.12 (± 0.319)	0.04 (± 0.374)	0.02 (± 0.098)	0.25 (± 0.226)
Change D1 - 4h post-morning dose - Baseline	-0.07 (± 0.367)	0.08 (± 0.276)	0.13 (± 0.225)	0.38 (± 0.264)
Change D8 - pre-morning dose - Baseline	0.08 (± 0.306)	-0.16 (± 0.302)	0.07 (± 0.234)	0.02 (± 0.392)
Change D8 - 4h post-morning dose - Baseline	0.00 (± 0.415)	0.01 (± 0.304)	0.00 (± 0.179)	0.20 (± 0.335)
Change D15 - pre-morning dose - Baseline	0.12 (± 0.449)	-0.23 (± 0.266)	0.15 (± 0.266)	0.10 (± 0.292)
Change D15 - 4h post-morning dose - Baseline	0.22 (± 0.799)	0.05 (± 0.424)	0.10 (± 0.237)	0.28 (± 0.327)
Change Follow-up - Baseline	0.07 (± 0.308)	0.00 (± 0.00)	0.02 (± 0.133)	-0.08 (± 0.475)

Notes:

[15] - Change Follow-up C - Baseline (n=2) not avialbale, therefore stated 0.00

[16] - subjects day 15 changes:n=5

End point values	Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: celcius				
arithmetic mean (standard deviation)				
Change D1 - 1h post-morning dose - Baseline	-0.02 (± 0.256)			
Change D1 - 4h post-morning dose - Baseline	0.02 (± 0.248)			
Change D8 - pre-morning dose - Baseline	-0.08 (± 0.462)			
Change D8 - 4h post-morning dose - Baseline	0.02 (± 0.488)			
Change D15 - pre-morning dose - Baseline	-0.03 (± 0.339)			
Change D15 - 4h post-morning dose - Baseline	-0.05 (± 0.226)			
Change Follow-up - Baseline	0.10 (± 0.341)			

Statistical analyses

No statistical analyses for this end point

Secondary: renal clearance from plasma (CLr)

End point title	renal clearance from plasma (CLr)[17]

End point description:

End point type	Secondary

End point timeframe:

day 15, 0-12h

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo values not reported

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	4	6
Units: l/h				
geometric mean (standard deviation)				
CLR d15, 0-12h	2.604 (± 1.412)	2.502 (± 1.966)	3.482 (± 1.367)	2.092 (± 1.263)

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of POL6014 after q.d. dosing

End point title	Tmax of POL6014 after q.d. dosing[18]

End point description:

End point type	Secondary

End point timeframe:

on D1,D15 and D28 (only Cohort C)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.
cmaxDue to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[19]	6[20]	6	
Units: hour				
geometric mean (standard deviation)				
Day 1	1.787 (± 1.318)	1.904 (± 1.426)	1.904 (± 1.426)	
Day 15	1.261 (± 1.735)	2.152 (± 1.581)	1.523 (± 1.605)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	1.620 (± 1.428)	

Notes:

[19] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[20] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of POL6014after QD dosing

End point title	Cmax of POL6014after QD dosing[21]

End point description:

End point type	Secondary

End point timeframe:

on day 1, day 15, day 28 (Cohort C only)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[22]	6[23]	6	
Units: ng/ml				
geometric mean (standard deviation)				
Day 1	74.36 (± 2.290)	297.0 (± 1.685)	69.77 (± 1.390)	
Day 15	91.56 (± 1.600)	263.3 (± 1.842)	69.76 (± 1.496)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	82.25 (± 1.543)	

Notes:

[22] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[23] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

Statistical analysis title	ANOVA of Cmax,D15 and dose after q.d. dosing

Statistical analysis description:

ANOVA of Cmax,D15 and dose after q.d. dosing

Comparison groups	Cohort 2A (160mg/day) v Cohort 1A-(80 mg/day)

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.0024 [25]
Method	ANOVA

Notes:

[24] - other

[25] - comparison 160mg QD : 80mg QD

Secondary: Cmax,norm of POL6014 after q.d. dosing

End point title	Cmax,norm of POL6014 after q.d. dosing[26]

End point description:

End point type	Secondary

End point timeframe:

on day 1, day 15 and day 28 (Cohort C only)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[27]	6[28]	6	
Units: ng/mL/(mg/kg)				
geometric mean (standard deviation)				
Day 1	68.62 (± 2.049)	146.8 (± 1.800)	124.0 (± 1.560)	
Day 15	84.48 (± 1.553)	130.1 (± 2.009)	123.9 (± 1.620)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	146.1 (± 1.593)	

Notes:

[27] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[28] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: AUCτ of POL6014 after q.d. dosing

End point title	AUCτ of POL6014 after q.d. dosing[29]

End point description:

End point type	Secondary

End point timeframe:

on day 1, day 15, day 28 (cohort C only)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[30]	6[31]	6	
Units: h*ng/ml				
geometric mean (standard deviation)				
Day 1	513.2 (± 2.249)	1971 (± 1.614)	471.7 (± 1.407)	
Day 15	559.0 (± 1.726)	1636 (± 1.787)	437.5 (± 1.787)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	562.3 (± 1.386)	

Notes:

[30] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[31] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: AUCτ,norm of POL6014 after q.d. dosing

End point title	AUCτ,norm of POL6014 after q.d. dosing[32]

End point description:

End point type	Secondary

End point timeframe:

on day 1, day 15 and day 28 (Cohort C only)

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[33]	6[34]	6	
Units: h*ng/mL/(mg/kg)				
geometric mean (standard deviation)				
Day 1	473.6 (± 1.986)	974.2 (± 1.714)	838.0 (± 1.552)	
Day 15	515.8 (± 1.597)	808.4 (± 1.961)	777.3 (± 1.501)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	999.1 (± 1.411)	

Notes:

[33] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[34] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: Aeт of POL6014 after q.d. dosing

End point title	Aeт of POL6014 after q.d. dosing[35]

End point description:

End point type	Secondary

End point timeframe:

d1,d15 and d28

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[36]	6[37]	6[38]	
Units: microgram(s)				
geometric mean (standard deviation)				
day 1,0-12h	1301 (± 2.402)	6070 (± 2.163)	942.1 (± 1.382)	
day 1,12-24h	0.00 (± 0.00)	631.9 (± 1.839)	109.5 (± 1.299)	
day 15, 0-12h	1456 (± 1.734)	4093 (± 2.465)	1075 (± 1.427)	
day 15, 12-24h	215.7 (± 1.288)	1328 (± 3.297)	1.217 (± 1.357)	
day 28, 0-12h	0.00 (± 0.00)	0.00 (± 0.00)	1176 (± 1.347)	
day 28,12-24h	0.00 (± 0.00)	0.00 (± 0.00)	119.9 (± 1.957)	

Notes:

[36] - D1 0-12h:N=6
D1 12-24h:N=2
D15 0-12h:N=6
D15 12-24h:N=3
D1,12-24h not available,no D28 treatment

[37] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[38] - Day 1 0-12h:N=6
Day 1 12-24h:N=3
D15 0-12h:N=6
D15 12-24h:N=3
D28 0-12h:N=6
D28 12-24h:N=3

Statistical analyses

No statistical analyses for this end point

Secondary: %Aeт,D1 of POL6014

End point title	%Aeт,D1 of POL6014[39]

End point description:

End point type	Secondary

End point timeframe:

day 1

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no placebo values reported

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[40]	6	6	6[41]
Units: percent				
geometric mean (standard deviation)				
day 1,0-12h	1.626 (± 2.402)	3.794 (± 2.163)	3.195 (± 2.380)	2.355 (± 1.382)
day 1,12-24h	0.00 (± 0.00)	0.395 (± 1.839)	2.287 (± 1.969)	0.274 (± 1.299)

Notes:

[40] - day 1,12-24h: N=2

[41] - day1,12-24h: N=3

Statistical analyses

No statistical analyses for this end point

Secondary: AUCт of POL6014 after b.i.d. dosing

End point title	AUCт of POL6014 after b.i.d. dosing[42]

End point description:

End point type	Secondary

End point timeframe:

on day 15

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: [h*ng/ml]				
geometric mean (standard deviation)				
day 15 moning	663.1 (± 2.102)			
day 15 evening	734.1 (± 1.560)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCτ,norm of POL6014 after b.i.d. dosing

End point title	AUCτ,norm of POL6014 after b.i.d. dosing[43]

End point description:

End point type	Secondary

End point timeframe:

trial duration

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: [h*ng/ml]				
geometric mean (standard deviation)				
day 15 moning	488.8 (± 2.946)			
day 15 evening	586.0 (± 1.747)			
day 1 morning	546 (± 2.350)			
day 1 evening	611.6 (± 1.619)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of POL6014 after b.i.d. dosing

End point title	Cmax of POL6014 after b.i.d. dosing[44]

End point description:

End point type	Secondary

End point timeframe:

day 15

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (standard deviation)				
day15 morning day 15 evening	101.8 (± 2.987) 115.2 (± 1.997)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax,norm of POL6014 after b.i.d. dosing

End point title	Cmax,norm of POL6014 after b.i.d. dosing[45]

End point description:

End point type	Secondary

End point timeframe:

day 15

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: [ng/mL/mg/kg)]				
geometric mean (standard deviation)				
day 15 morning day 15 evening	79.16 (± 2.979) 98.58 (± 1.984)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of POL6014 after b.i.d. dosing

End point title	Tmax of POL6014 after b.i.d. dosing[46]

End point description:

End point type	Secondary

End point timeframe:

on day 15

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: hour				
geometric mean (standard deviation)				
day 15 morning	1.151 (± 1.368)			
day 15 evening	1.001 (± 1.127)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of POL6014 after b.i.d. dosing

End point title	Cmin of POL6014 after b.i.d. dosing[47]

End point description:

End point type	Secondary

End point timeframe:

on day 15

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/ml				
geometric mean (standard deviation)				
day 15 morning	7.187 (± 2.078)			
day 15 evening	25.84 (± 2.678)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cav of POL6014 after b.i.d. dosing

End point title	Cav of POL6014 after b.i.d. dosing[48]

End point description:

End point type	Secondary

End point timeframe:

day 15

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/ml				
geometric mean (standard deviation)				
day 15 morning	2.946 (± 148.8)			
day 15 evening	1.747 (± 60.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Aeт of POL6014 after b.i.d. dosing

End point title	Aeт of POL6014 after b.i.d. dosing[49]

End point description:

End point type	Secondary

End point timeframe:

day 15

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	5[50]			
Units: microgram(s)				
geometric mean (standard deviation)				
day 15 morning	2549 (± 2.330)			
day 15 evening	1268 (± 4.381)			

Notes:

[50] - D15 morning:N=4
D15 evening:N=5

Statistical analyses

No statistical analyses for this end point

Secondary: CLR of POL6014 after b.i.d. dosing

End point title	CLR of POL6014 after b.i.d. dosing[51]

End point description:

End point type	Secondary

End point timeframe:

day 15

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 2B (160mg/day)			
Subject group type	Reporting group			
Number of subjects analysed	4[52]			
Units: L/h				
geometric mean (standard deviation)				
day 15 morning	3.482 (± 1.367)			
day 15 evening	2.165 (± 3.153)			

Notes:

[52] - day 15 evening:N=5

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of POL6014 after q.d. dosing

End point title	Cmin of POL6014 after q.d. dosing[53]

End point description:

End point type	Secondary

End point timeframe:

Day15 and Day 28

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[54]	6[55]	6	
Units: ng/ml				
geometric mean (standard deviation)				
Day 15	2.836 (± 1.574)	5.410 (± 1.473)	1.945 (± 2.387)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	1.209 (± 1.266)	

Notes:

[54] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[55] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: Cav of POL6014 after q.d. dosing

End point title	Cav of POL6014 after q.d. dosing[56]

End point description:

End point type	Secondary

End point timeframe:

Day 15 and Day 28 (cohort C only)

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.
Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[57]	6[58]	6	
Units: ng/ml				
geometric mean (standard deviation)				
Day 15	23.29 (± 1.726)	68.16 (± 1.787)	18.23 (± 1.385)	
Day 28	0.00 (± 0.00)	0.00 (± 0.00)	23.43 (± 1.386)	

Notes:

[57] - As per protocol Cohort A did not have a Day28 dosing , hence no results are included (0.00).

[58] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

Statistical analyses

No statistical analyses for this end point

Secondary: %PTF of POL6014

End point title	%PTF of POL6014[59]

End point description:

End point type	Secondary

End point timeframe:

day 15 and day 28 (cohort C only)

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort 2B (160mg/day)	Cohort C
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5[60]	6
Units: percent				
geometric mean (standard deviation)				
day 15	378.0 (± 1.260)	376.6 (± 1.333)	26.68 (± 228.3)	364.1 (± 1.201)
day 28	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	345.8 (± 1.201)

Notes:

[60] - %PTF evening dose day 15: 88.55/SD4.804

Statistical analyses

No statistical analyses for this end point

Secondary: CLR of POL6014 after q.d. dosing

End point title	CLR of POL6014 after q.d. dosing[61]

End point description:

End point type	Secondary

End point timeframe:

day 15 and day 28

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to BD dosing in Cohort 2 B and registry limitations reflecting different dosing time points cohorts 1A, 2A and C (all OD dosing) are reflected in a separate EP entry.

Placebo values not reported.

End point values	Cohort 1A-(80 mg/day)	Cohort 2A (160mg/day)	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6[62]	6[63]	6[64]	
Units: litre/hour				
geometric mean (standard deviation)				
day 15, 0-12h	2.604 (± 1.412)	2.502 (± 1.966)	2.458 (± 1.299)	
day 15 12-24h	0.254 (± 1.407)	0.812 (± 2.285)	0.221 (± 1.359)	
day 28, 0-12h	0.00 (± 0.00)	0.00 (± 0.00)	2.092 (± 1.263)	
day 28 12-24h	0.00 (± 0.00)	0.00 (± 0.00)	0.204 (± 1.683)	

Notes:

[62] - day15 0-12h N=6
day15 12-24h N=3
As per protocol Cohort A did not have a Day28 dosing.
[63] - As per protocol Cohort 2A did not have a Day28 dosing , hence no results are included (0.00).

[64] - day 15 0-12hN=6
day 15 12-24hN=3
day 28 0-12hN=6
day 28 12-24hN=3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Comprehensive assessment of any apparent toxicity experienced by the patient will be performed throughout the course of the trial, from the time of the patient's signature of informed consent till the final study visit.

Adverse event reporting additional description:

No SAEs were reported during the whole study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Cohort 1A -80mgQD
Reporting group description: -	
Reporting group title	Cohort 2A-160mgQD
Reporting group description: -	
Reporting group title	Cohort 2B - 80mgBID
Reporting group description: -	
Reporting group title	Cohort C- 40mgQD
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Total

Reporting group description: -

Serious adverse events	Cohort 1A -80mgQD	Cohort 2A-160mgQD	Cohort 2B - 80mgBID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort C- 40mgQD	Placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cohort 1A -80mgQD	Cohort 2A-160mgQD	Cohort 2B - 80mgBID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	3 / 6 (50.00%)	6 / 6 (100.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Forced expiratory flow decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	0	2	4
Intercostal neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	1	1	6
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	3	2	1
Dyspnoea			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	4 / 6 (66.67%)
occurrences (all)	2	1	6
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Increased viscosity of upper respiratory secretion			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Obstructive airways disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	5
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Pharyngeal paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Sputum increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Sputum retention			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	4	2	1
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Product issues			
Product taste abnormal			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	3	1

Non-serious adverse events	Cohort C- 40mgQD	Placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	7 / 8 (87.50%)	26 / 32 (81.25%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Forced expiratory flow decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	2

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	3 / 8 (37.50%)	8 / 32 (25.00%)
occurrences (all)	0	3	9
Intercostal neuralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 32 (15.63%)
occurrences (all)	0	0	8
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 32 (6.25%)
occurrences (all)	1	1	2
Eructation			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	2 / 32 (6.25%)
occurrences (all)	1	1	2
Flatulence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	2
Vomiting			

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	6 / 32 (18.75%)
occurrences (all)	2	0	8
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	8 / 32 (25.00%)
occurrences (all)	1	0	11
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	2 / 6 (33.33%)	0 / 8 (0.00%)	3 / 32 (9.38%)
occurrences (all)	2	0	3
Increased viscosity of upper respiratory secretion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Obstructive airways disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	5
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	3 / 32 (9.38%)
occurrences (all)	1	0	3
Pharyngeal paraesthesia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	2
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Sputum increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	4 / 32 (12.50%)
occurrences (all)	0	1	4
Sputum retention			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	2
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	2 / 32 (6.25%)
occurrences (all)	1	0	2
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	5 / 32 (15.63%)
occurrences (all)	0	0	7
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Product issues			
Product taste abnormal			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	6 / 32 (18.75%)
occurrences (all)	1	0	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2018	Amendment 1 resulted in protocol Version 2.0. The main changes implemented are listed below: - Clarification on different procedures required by the protocol - Addition of Appendix 2 to explain the "Guidance for DMC Assessment Criteria" - Clarification of sputum bacteriology assessments timing in Appendix 1 - Change of the interval for screening from D-21 to D-1 to D-21 to D-10
20 August 2019	Amendment 2 resulted in protocol Version 3.0. The main change implemented is listed below: - Analysis of the unblinded data was performed by the Sponsor at the end of each cohort. Accordingly, text was modified in Sections 3.1, 5.4, 9, 9.6, and 11.1.
03 March 2020	Amendment 3 resulted in protocol Version 4.0. The main changes implemented are listed below: - Modification and renaming of pre-planned Cohort 1B to Cohort C, at lower dose of 40 mg QD in 8 patients (6 on verum, 2 on placebo) for 28 days instead of 40 mg BID in 16 patients for 15 days. The respective sections on study design and schedule of assessment were updated. - Complete removal of DL3 (320 mg daily) as well as study Part II which had been provisionally kept but not precisely defined so far - Modification of inclusion criterion no.7 (applicable to upcoming Cohort C): patient had to have an FEV1% predicted value at screening ≥50% instead of 40% to decrease potential risk and impact in case of FEV1 decline. - Inclusion of additional criteria related to lung function for AE/SAE grading and patient discontinuation from the IMP - Summary information from unblinded interim data of completed Cohorts 1A, 2A, and 2B had been incorporated to the protocol (especially benefit-risk assessment) to inform about further conduct of the study by investigators.
23 June 2020	Amendment 4 resulted in protocol Version 5.0. The main change implemented is listed below: - Administrative change: Dr. med. O. Kornmann (IKF Pneumologie GmbH & Co. KG) replaced Dr. med. W. Timmer (Inamed GmbH) as Coordinating Investigator

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported