



## Clinical trial results:

### Phase-Ib/Ila 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   |
| Public contact               | Julien Gaudias, Santhera Pharmaceuticals (Switzerland) Ltd, +41 798110198, julien.gaudias@santhera.com |
| Scientific contact           | Julien Gaudias, Santhera Pharmaceuticals (Switzerland) Ltd, +41 798110198, julien.gaudias@santhera.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 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                   |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | 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:<br>160 mg QD lonodelestat or matching placebo for 15 days, Inhalation use |                       |
| <b>Arm title</b>   | 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

|                  |          |
|------------------|----------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | 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          | -                     | -       | -                     |

| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>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:<br>Placebo  |                       |
| Reporting group title  | Cohort 2A (160mg/day) |
| Reporting group description:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>Local irritation of the nose or pharynx by visual inspection and symptomatology                           |   |
| End point type  | Primary   |
| End point timeframe:<br>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 <sup>[2]</sup> |
|-----------------|--|

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 <sup>[3]</sup> |
|-----------------|--|

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 <sup>[4]</sup> | 6                     | 6 <sup>[5]</sup>      |
| 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 <sup>[6]</sup> |
|-----------------|--|

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 <sup>[7]</sup> |
| 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 <sup>[8]</sup> |
|-----------------|---|

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 <sup>[9]</sup> |
| End point description:                |   |
| ECG Mean Ventricular Rate [beats/min] |   |
| End point type                        | Primary   |
| End point timeframe:                  |   |
| trial duration                        |   |

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 <sup>[10]</sup> |
|-----------------|---|

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) <sup>[11]</sup>   |
| 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 <sup>[12]</sup> | 6                     | 6 <sup>[13]</sup>     |
| 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) <sup>[14]</sup>   |
| 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 <sup>[15]</sup> | 6                     | 6 <sup>[16]</sup>     |
| 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) <sup>[17]</sup> |
|-----------------|---|

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 <sup>[18]</sup> |
| 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 <sup>[19]</sup>     | 6 <sup>[20]</sup>     | 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 <sup>[21]</sup> |
|-----------------|--|

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 <sup>[22]</sup>     | 6 <sup>[23]</sup>     | 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 <sup>[24]</sup>    |
| P-value                                 | = 0.0024 <sup>[25]</sup> |
| 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 <sup>[26]</sup> |
| 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 <sup>[27]</sup>     | 6 <sup>[28]</sup>     | 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: AUC<sub>T</sub> of POL6014 after q.d. dosing

|                        |   |
|------------------------|---|
| End point title        | AUC <sub>T</sub> of POL6014 after q.d. dosing <sup>[29]</sup> |
| 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 <sup>[30]</sup>     | 6 <sup>[31]</sup>     | 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: AUC<sub>T</sub>,norm of POL6014 after q.d. dosing

|   |   |
|---|---|
| End point title                             | AUC <sub>T</sub> ,norm of POL6014 after q.d. dosing <sup>[32]</sup> |
| 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 <sup>[33]</sup>     | 6 <sup>[34]</sup>     | 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: Aet of POL6014 after q.d. dosing

|                 |  |
|-----------------|--|
| End point title | Aet of POL6014 after q.d. dosing <sup>[35]</sup> |
|-----------------|--|

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 <sup>[36]</sup>     | 6 <sup>[37]</sup>     | 6 <sup>[38]</sup> |  |
| 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: %Aet,D1 of POL6014

|                 |                                    |
|-----------------|------------------------------------|
| End point title | %Aet,D1 of POL6014 <sup>[39]</sup> |
|-----------------|------------------------------------|

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 <sup>[40]</sup>     | 6                     | 6                     | 6 <sup>[41]</sup> |
| 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: AUC<sub>T</sub> of POL6014 after b.i.d. dosing

|                        |   |
|------------------------|---|
| End point title        | AUC <sub>T</sub> of POL6014 after b.i.d. dosing <sup>[42]</sup> |
| 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: AUC<sub>T</sub>,norm of POL6014 after b.i.d. dosing

End point title AUC<sub>T</sub>,norm of POL6014 after b.i.d. dosing<sup>[43]</sup>

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<br>(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 (±<br>2.946)       |  |  |  |
| day 15 evening                      | 586.0 (±<br>1.747)       |  |  |  |
| day 1 morning                       | 546 (± 2.350)            |  |  |  |
| day 1 evening                       | 611.6 (±<br>1.619)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: C<sub>max</sub> of POL6014 after b.i.d. dosing

End point title C<sub>max</sub> of POL6014 after b.i.d. dosing<sup>[44]</sup>

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.

|                                     |                          |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>             | Cohort 2B<br>(160mg/day) |  |  |  |
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 6                        |  |  |  |
| Units: ng/mL                        |                          |  |  |  |
| geometric mean (standard deviation) |                          |  |  |  |
| day15 morning                       | 101.8 (±<br>2.987)       |  |  |  |
| day 15 evening                      | 115.2 (±<br>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 <sup>[45]</sup> |
|-----------------|--|

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.

|                                     |                          |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>             | Cohort 2B<br>(160mg/day) |  |  |  |
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 5                        |  |  |  |
| Units: [ng/mL/mg/kg]]               |                          |  |  |  |
| geometric mean (standard deviation) |                          |  |  |  |
| day 15 morning                      | 79.16 (±<br>2.979)       |  |  |  |
| day 15 evening                      | 98.58 (±<br>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 <sup>[46]</sup> |
|-----------------|---|

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<br>(160mg/day) |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 5                        |  |  |  |
| Units: hour                         |                          |  |  |  |
| geometric mean (standard deviation) |                          |  |  |  |
| day 15 morning                      | 1.151 (±<br>1.368)       |  |  |  |
| day 15 evening                      | 1.001 (±<br>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 <sup>[47]</sup> |
| 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<br>(160mg/day) |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 5                        |  |  |  |
| Units: ng/ml                        |                          |  |  |  |
| geometric mean (standard deviation) |                          |  |  |  |
| day 15 morning                      | 7.187 (±<br>2.078)       |  |  |  |
| day 15 evening                      | 25.84 (±<br>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<sup>[48]</sup>

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<br>(160mg/day) |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 5                        |  |  |  |
| Units: ng/ml                        |                          |  |  |  |
| geometric mean (standard deviation) |                          |  |  |  |
| day 15 morning                      | 2.946 (±<br>148.8)       |  |  |  |
| day 15 evening                      | 1.747 (±<br>60.44)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Aet of POL6014 after b.i.d. dosing

End point title Aet of POL6014 after b.i.d. dosing<sup>[49]</sup>

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.

|                                     |                          |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>             | Cohort 2B<br>(160mg/day) |  |  |  |
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 5 <sup>[50]</sup>        |  |  |  |
| 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 <sup>[51]</sup> |
|-----------------|--|

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.

|                                     |                          |  |  |  |
|-------------------------------------|--------------------------|--|--|--|
| <b>End point values</b>             | Cohort 2B<br>(160mg/day) |  |  |  |
| Subject group type                  | Reporting group          |  |  |  |
| Number of subjects analysed         | 4 <sup>[52]</sup>        |  |  |  |
| 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 <sup>[53]</sup> |
|-----------------|---|

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 <sup>[54]</sup>     | 6 <sup>[55]</sup>     | 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<sup>[56]</sup>

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 <sup>[57]</sup>     | 6 <sup>[58]</sup>     | 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<sup>[59]</sup>

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 <sup>[60]</sup>     | 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<sup>[61]</sup>

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 <sup>[62]</sup>     | 6 <sup>[63]</sup>     | 6 <sup>[64]</sup> |  |
| 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              |

| <b>Non-serious adverse events</b>                     | 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              |
| Eruption   |                |                |                |
| 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              |

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 6 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 5 / 32 (15.63%)<br>7 |
| Rash pustular<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 1 / 32 (3.13%)<br>1  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)              | 0 / 6 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 32 (3.13%)<br>1  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 1 / 32 (3.13%)<br>1  |
| Product issues<br>Product taste abnormal<br>subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 6 / 32 (18.75%)<br>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: <ul style="list-style-type: none"><li>- Clarification on different procedures required by the protocol</li><li>- Addition of Appendix 2 to explain the "Guidance for DMC Assessment Criteria"</li><li>- Clarification of sputum bacteriology assessments timing in Appendix 1</li><li>- Change of the interval for screening from D-21 to D-1 to D-21 to D-10</li></ul>  |
| 20 August 2019    | Amendment 2 resulted in protocol Version 3.0. The main change implemented is listed below: <ul style="list-style-type: none"><li>- 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.</li></ul>  |
| 03 March 2020     | Amendment 3 resulted in protocol Version 4.0. The main changes implemented are listed below: <ul style="list-style-type: none"><li>- 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.</li><li>- Complete removal of DL3 (320 mg daily) as well as study Part II which had been provisionally kept but not precisely defined so far</li><li>- Modification of inclusion criterion no.7 (applicable to upcoming Cohort C): patient had to have an FEV1% predicted value at screening <math>\geq 50\%</math> instead of 40% to decrease potential risk and impact in case of FEV1 decline.</li><li>- Inclusion of additional criteria related to lung function for AE/SAE grading and patient discontinuation from the IMP</li><li>- 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.</li></ul> |
| 23 June 2020      | Amendment 4 resulted in protocol Version 5.0. The main change implemented is listed below: <ul style="list-style-type: none"><li>- Administrative change: Dr. med. O. Kornmann (IKF Pneumologie GmbH &amp; Co. KG) replaced Dr. med. W. Timmer (Inamed GmbH) as Coordinating Investigator</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported