



## Clinical trial results:

**A subject-, investigator-, and sponsor-blinded, randomized, placebo-controlled, multicenter study to investigate efficacy, safety, and tolerability of VAY736 in patients with idiopathic pulmonary fibrosis**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2017-002667-17   |
| Trial protocol           | GB IE DE IT FR   |
| Global end of trial date | 14 February 2022 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 02 March 2023 |
| First version publication date | 02 March 2023 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CVAY736X2207 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03287414 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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                       | 14 February 2022 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 February 2022 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of VAY736 in patients with IPF by looking at the change from baseline to end-of-treatment (48 weeks of treatment) in forced vital capacity (FVC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 20 December 2017 |
| 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 | Canada: 1         |
| Country: Number of subjects enrolled | Germany: 8        |
| Country: Number of subjects enrolled | Ireland: 5        |
| Country: Number of subjects enrolled | Italy: 4          |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | United States: 10 |
| Worldwide total number of subjects   | 30                |
| EEA total number of subjects         | 17                |

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)      | 8  |
| From 65 to 84 years       | 22 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted across 16 centers in 6 countries.

### Pre-assignment

Screening details:

A total of 142 participants were screened of which 30 participants were randomized. 1 participant in the VAY736 arm did not receive treatment as the patient withdrew consent before first dosing.

### Period 1

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

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| <b>Arm title</b>             | VAY736 |

Arm description:

Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

|  |                  |
|--|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ianalumab        |
| Investigational medicinal product code | VAY736sub        |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks

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

Arm description:

Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

|  |                  |
|--|------------------|
| Arm type                               | Placebo          |
| Investigational medicinal product name | Placebo          |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Subcutaneous use |

Dosage and administration details:

Placebo administered subcutaneously every 4 weeks for 48 weeks

| <b>Number of subjects in period 1<sup>[1]</sup></b> | VAY736 | Placebo |
|---|--------|---------|
| Started   | 13     | 16      |
| Completed   | 6      | 12      |
| Not completed                                       | 7      | 4       |
| Study terminated by Sponsor                         | 2      | 2       |
| Discontinued early with reason "other" selected     | 1      | 1       |
| Adverse event, non-fatal                            | -      | 1       |
| Subject/Guardian decision                           | 4      | -       |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 1 participant randomized was never treated

## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | VAY736 |
|-----------------------|--------|

Reporting group description:

Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

| Reporting group values                             | VAY736 | Placebo | Total |
|--|--------|---------|-------|
| Number of subjects                                 | 13     | 16      | 29    |
| Age categorical                                    |        |         |       |
| Units: Subjects                                    |        |         |       |
| In utero   | 0      | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0      | 0       | 0     |
| Newborns (0-27 days)                               | 0      | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0      | 0       | 0     |
| Children (2-11 years)                              | 0      | 0       | 0     |
| Adolescents (12-17 years)                          | 0      | 0       | 0     |
| Adults (18-64 years)                               | 3      | 5       | 8     |
| From 65-84 years                                   | 10     | 11      | 21    |
| 85 years and over                                  | 0      | 0       | 0     |
| Age continuous                                     |        |         |       |
| Units: years                                       |        |         |       |
| arithmetic mean                                    | 69.7   | 68.3    |       |
| standard deviation                                 | ± 9.30 | ± 8.15  | -     |
| Gender categorical                                 |        |         |       |
| Units: Subjects                                    |        |         |       |
| Female   | 1      | 1       | 2     |
| Male   | 12     | 15      | 27    |
| Race/Ethnicity                                     |        |         |       |
| Units: Subjects                                    |        |         |       |
| White  | 13     | 16      | 29    |

## End points

### End points reporting groups

|   |         |
|---|---------|
| Reporting group title   | VAY736  |
| Reporting group description:<br>Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy |         |
| Reporting group title   | Placebo |
| Reporting group description:<br>Participants received placebo administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy       |         |

### Primary: Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC)

|  |   |
|--|---|
| End point title  | Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC) |
| End point description:<br>FVC was defined as the maximum amount of air that an individual was able to forcibly exhale from his / her lungs after taking the deepest breath they could. Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date. |   |
| End point type   | Primary   |
| End point timeframe:<br>From baseline up to 48 weeks post first dose of study treatment  |   |

| End point values                    | VAY736                | Placebo                |  |  |
|-------------------------------------|-----------------------|------------------------|--|--|
| Subject group type                  | Reporting group       | Reporting group        |  |  |
| Number of subjects analysed         | 3                     | 16                     |  |  |
| Units: Liter (L)                    |                       |                        |  |  |
| least squares mean (standard error) | 0.039 ( $\pm$ 0.1116) | -0.023 ( $\pm$ 0.0773) |  |  |

### Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Change from baseline in FVC |
| Comparison groups          | VAY736 v Placebo            |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 19                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           |                               |
| P-value                                 | = 0.3248 <sup>[1]</sup>       |
| Method                                  | MMRM                          |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | 0.063                         |
| Confidence interval                     |                               |
| level                                   | Other: 80 %                   |
| sides                                   | 2-sided                       |
| lower limit                             | -0.115                        |
| upper limit                             | 0.241                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.1379                        |

Notes:

[1] - 1-sided p-values were obtained using MMRM Model.

### Secondary: Percentage of participants with all-cause mortality events

|   |  |
|---|--|
| End point title   | Percentage of participants with all-cause mortality events |
| End point description:  |  |
| All-cause mortality events were defined as deaths due to any cause. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Up to 48 weeks post first dose of study treatment   |  |

| End point values                  | VAY736              | Placebo           |  |  |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed       | 12                  | 16                |  |  |
| Units: Percentage of participants |                     |                   |  |  |
| number (confidence interval 80%)  | 8.3 (2.39 to 26.92) | 0 (-9999 to 9999) |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Survival Analysis: All-cause mortality |
| Comparison groups                       | VAY736 v Placebo                       |
| Number of subjects included in analysis | 28                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | other                                  |
| P-value                                 | = 0.868                                |
| Method                                  | Logrank                                |



**Secondary: Percentage of participants with survival Idiopathic Pulmonary Fibrosis (IPF) -related mortality events**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with survival Idiopathic Pulmonary Fibrosis (IPF) -related mortality events |
|-----------------|--|

End point description:

IPF-related mortality events were defined as deaths due to IPF related cause. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 48 weeks post first dose of study treatment

| End point values                  | VAY736            | Placebo           |  |  |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed       | 12                | 16                |  |  |
| Units: Percentage of participants |                   |                   |  |  |
| number (confidence interval 80%)  | 0 (-9999 to 9999) | 0 (-9999 to 9999) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of participants with Progression-free survival (PFS) events**

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with Progression-free survival (PFS) events |
|-----------------|--|

End point description:

PFS events were divided into: 1) PFS1 events including progression (relative reduction in FVC  $\geq 10\%$ ) or death due to all causes, and 2) PFS2 events including progression (relative reduction in FVC  $\geq 10\%$ ) or death due to IPF-related causes. Kaplan-Meier estimates of the percentage of participants with the event of interest (PFS1 events or PFS2 events) along with 80% two-sided confidence intervals using Greenwood's formula are provided.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 48 weeks post first dose of study treatment

| End point values                  | VAY736                | Placebo               |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 12                    | 16                    |  |  |
| Units: Percentage of participants |                       |                       |  |  |
| number (confidence interval 80%)  |                       |                       |  |  |
| PFS1                              | 61.0 (38.22 to 84.20) | 31.9 (18.04 to 52.51) |  |  |
| PFS2                              | 57.1 (33.44 to 82.86) | 31.9 (18.04 to 52.51) |  |  |

## Statistical analyses

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Survival analysis: PFS1 |
| Comparison groups                       | VAY736 v Placebo        |
| Number of subjects included in analysis | 28                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.921                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 2.6                     |
| Confidence interval                     |                         |
| level                                   | Other: 80 %             |
| sides                                   | 2-sided                 |
| lower limit                             | 1.1                     |
| upper limit                             | 6.3                     |

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Survival analysis: PFS2 |
| Comparison groups                       | VAY736 v Placebo        |
| Number of subjects included in analysis | 28                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.863                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 2.2                     |
| Confidence interval                     |                         |
| level                                   | Other: 80 %             |
| sides                                   | 2-sided                 |
| lower limit                             | 0.9                     |
| upper limit                             | 5.6                     |

## Secondary: Percentage of participants with disease progression events

|  |  |
|--|--|
| End point title  | Percentage of participants with disease progression events |
| End point description:<br>The following disease progression events were considered: a) relative reduction in FVC $\geq$ 10%; b) relative reduction in Diffusing Capacity of the Lungs (DLCO) $\geq$ 15%; c) absolute reduction in Six Minute Walk Distance (6MWD) $\geq$ 50 m. Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided. |  |
| End point type   | Secondary  |

End point timeframe:

Up to 48 weeks post first dose of study treatment

| End point values                  | VAY736                | Placebo               |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 12                    | 16                    |  |  |
| Units: Percentage of participants |                       |                       |  |  |
| number (confidence interval 80%)  |                       |                       |  |  |
| FVC                               | 57.1 (33.44 to 82.86) | 31.9 (18.08 to 52.51) |  |  |
| DLCO                              | 73.8 (46.56 to 92.24) | 56.1 (36.65 to 75.10) |  |  |
| 6MWD                              | 38.3 (19.96 to 64.88) | 75.0 (58.52 to 88.74) |  |  |

### Statistical analyses

| Statistical analysis title              | Survival Analysis: FVC |
|---|------------------------|
| Comparison groups                       | Placebo v VAY736       |
| Number of subjects included in analysis | 28                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other                  |
| P-value                                 | = 0.863                |
| Method                                  | Logrank                |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 2.2                    |
| Confidence interval                     |                        |
| level                                   | Other: 80 %            |
| sides                                   | 2-sided                |
| lower limit                             | 0.9                    |
| upper limit                             | 5.6                    |

| Statistical analysis title              | Survival Analysis: DLCO |
|---|-------------------------|
| Comparison groups                       | VAY736 v Placebo        |
| Number of subjects included in analysis | 28                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.457                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.9                     |

|                     |             |
|---------------------|-------------|
| Confidence interval |             |
| level               | Other: 80 % |
| sides               | 2-sided     |
| lower limit         | 0.4         |
| upper limit         | 2           |

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>       | Survival Analysis: 6MWD |
| Comparison groups                       | VAY736 v Placebo        |
| Number of subjects included in analysis | 28                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.019                 |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.3                     |
| Confidence interval                     |                         |
| level                                   | Other: 80 %             |
| sides                                   | 2-sided                 |
| lower limit                             | 0.1                     |
| upper limit                             | 0.6                     |

### Secondary: Percentage of participants with composite events

|  |  |
|--|--|
| End point title  | Percentage of participants with composite events |
| End point description:   |  |
| Composite events were defined as: 1) death (all-cause mortality), or relative reduction in FVC $\geq$ 10%, or relative reduction in DLCO $\geq$ 15%, or relative reduction in 6MWD $\geq$ 50 m (composite endpoint 1); and 2) Death (IPF-related mortality), or relative reduction in FVC $\geq$ 10%, or relative reduction in DLCO $\geq$ 15%, or relative reduction in 6MWD $\geq$ 50 m (composite endpoint 2). Kaplan-Meier estimates of the percentage of participants with the event of interest along with 80% two-sided confidence intervals using Greenwood's formula are provided |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Up to 48 weeks post first dose of study treatment  |  |

| End point values                  | VAY736                | Placebo               |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed       | 12                    | 16                    |  |  |
| Units: Percentage of participants |                       |                       |  |  |
| number (confidence interval 80%)  |                       |                       |  |  |
| Composite Endpoint 1              | 81.0 (63.86 to 93.29) | 66.3 (50.84 to 81.18) |  |  |
| Composite Endpoint 2              | 79.2 (61.07 to 92.70) | 66.3 (50.84 to 81.18) |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Survival Analysis: Composite Endpoint 1 |
| Comparison groups                       | VAY736 v Placebo                        |
| Number of subjects included in analysis | 28                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other                                   |
| P-value                                 | = 0.611                                 |
| Method                                  | Logrank                                 |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.1                                     |
| Confidence interval                     |   |
| level                                   | Other: 80 %                             |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.6                                     |
| upper limit                             | 2                                       |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Survival Analysis: Composite Endpoint 2 |
| Comparison groups                       | VAY736 v Placebo                        |
| Number of subjects included in analysis | 28                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other                                   |
| P-value                                 | = 0.549                                 |
| Method                                  | Logrank                                 |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.1                                     |
| Confidence interval                     |   |
| level                                   | Other: 80 %                             |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.6                                     |
| upper limit                             | 1.9                                     |

## Secondary: Change from baseline to end of treatment epoch (48 weeks of treatment) in Diffusing Capacity of the Lungs

|                 |   |
|-----------------|---|
| End point title | Change from baseline to end of treatment epoch (48 weeks of treatment) in Diffusing Capacity of the Lungs |
|-----------------|---|

### End point description:

DLCO is a measurement to assess the lungs' ability to transfer gas from inspired air to the bloodstream. DLCO was determined according to ATS guidelines. Change from baseline to end of treatment epoch (48 weeks of treatment) in diffusing capacity of the lung for carbon monoxide (DLCO) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care

treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement.

Baseline was defined as the last available assessment pre-dose before or on randomization date.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From baseline up to 48 weeks post first dose of study treatment |           |

| End point values                            | VAY736                 | Placebo                |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                          | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                 | 3                      | 7                      |  |  |
| Units: milliliter/minute/millimeter Mercury |                        |                        |  |  |
| least squares mean (standard error)         | -1.954 ( $\pm$ 1.0816) | -1.033 ( $\pm$ 0.7244) |  |  |

## Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title              | Change from baseline in DLCO |
| Comparison groups                       | VAY736 v Placebo             |
| Number of subjects included in analysis | 10                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other                        |
| P-value                                 | = 0.7576 [2]                 |
| Method                                  | MMRM                         |
| Parameter estimate                      | Least Squares of the Mean    |
| Point estimate                          | -0.92                        |
| Confidence interval                     |                              |
| level                                   | Other: 80 %                  |
| sides                                   | 2-sided                      |
| lower limit                             | -2.615                       |
| upper limit                             | 0.774                        |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 1.3109                       |

Notes:

[2] - 1-sided p-values were obtained using MMRM Model.

## Secondary: Change from baseline to the end of treatment epoch (48 weeks of treatment) in 6-minute walk distance (6MWD)

|                 |   |
|-----------------|---|
| End point title | Change from baseline to the end of treatment epoch (48 weeks of treatment) in 6-minute walk distance (6MWD) |
|-----------------|---|

End point description:

A standardized 6-minute walk test (6MWT) was performed in accordance with the guidelines of the American Thoracic Society 2002. The distance walked in six minutes (6MWD) was recorded. Change from baseline to end of treatment epoch (48 weeks of treatment) in 6MWD was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement.

Baseline was defined as the last available assessment pre-dose before or on randomization date.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From baseline up to 48 weeks post first dose of study treatment |           |

|                                     |                        |                          |  |  |
|-------------------------------------|------------------------|--------------------------|--|--|
| <b>End point values</b>             | VAY736                 | Placebo                  |  |  |
| Subject group type                  | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed         | 2                      | 7                        |  |  |
| Units: Meter (m)                    |                        |                          |  |  |
| least squares mean (standard error) | 19.743 ( $\pm$ 19.743) | -12.479 ( $\pm$ 28.9400) |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Change from baseline in 6MWD |
| Comparison groups                       | VAY736 v Placebo             |
| Number of subjects included in analysis | 9                            |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other                        |
| P-value                                 | = 0.3018 <sup>[3]</sup>      |
| Method                                  | MMRM                         |
| Parameter estimate                      | Least Squares of the Mean    |
| Point estimate                          | 32.222                       |
| Confidence interval                     |                              |
| level                                   | Other: 80 %                  |
| sides                                   | 2-sided                      |
| lower limit                             | -47.572                      |
| upper limit                             | 112.015                      |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 61.8632                      |

Notes:

[3] - Change from baseline in 6MWD

### Secondary: Change from baseline to the end of treatment epoch (48 weeks of treatment) in distance saturation product

|                 |   |
|-----------------|---|
| End point title | Change from baseline to the end of treatment epoch (48 weeks of treatment) in distance saturation product |
|-----------------|---|

End point description:

Distance saturation product is the product of distance walked and lowest oxygen saturation during the 6-min walk test. Change from baseline to end of treatment epoch (48 weeks of treatment) in distance saturation product was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline up to 48 weeks post first dose of study treatment

| End point values                    | VAY736                 | Placebo                  |  |  |
|-------------------------------------|------------------------|--------------------------|--|--|
| Subject group type                  | Reporting group        | Reporting group          |  |  |
| Number of subjects analysed         | 2                      | 7                        |  |  |
| Units: Meter% (m%)                  |                        |                          |  |  |
| least squares mean (standard error) | 9.746 ( $\pm$ 52.2985) | -19.420 ( $\pm$ 28.3755) |  |  |

## Statistical analyses

|   |                             |
|---|-----------------------------|
| Statistical analysis title              | Distance saturation product |
| Comparison groups                       | VAY736 v Placebo            |
| Number of subjects included in analysis | 9                           |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other                       |
| P-value                                 | = 0.314 <sup>[4]</sup>      |
| Method                                  | MMRM                        |
| Parameter estimate                      | Least Squares of the Mean   |
| Point estimate                          | 29.166                      |
| Confidence interval                     |                             |
| level                                   | Other: 80 %                 |
| sides                                   | 2-sided                     |
| lower limit                             | -48.22                      |
| upper limit                             | 106.553                     |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 60.0143                     |

Notes:

[4] - 1-sided p-values were obtained using MMRM Model.

## Secondary: Change from baseline to the end of treatment epoch (48 weeks of treatment) in resting oxygen saturation level (on room air)

|                 |   |
|-----------------|---|
| End point title | Change from baseline to the end of treatment epoch (48 weeks of treatment) in resting oxygen saturation level (on room air) |
|-----------------|---|

End point description:

Change from baseline to end of treatment epoch (48 weeks of treatment) in resting oxygen saturation (on room air) was analyzed using a Mixed Effects Model for Repeated Measures (MMRM) and considering all assessments collected during the treatment epoch. The model included treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, or no treatment) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. A positive change from baseline indicates improvement. Baseline was defined as the last available assessment pre-dose before or on randomization date.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline up to 48 weeks post first dose of study treatment



| <b>End point values</b>             | VAY736                 | Placebo                |  |  |
|-------------------------------------|------------------------|------------------------|--|--|
| Subject group type                  | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed         | 5                      | 7                      |  |  |
| Units: Percentage (%)               |                        |                        |  |  |
| least squares mean (standard error) | -0.117 ( $\pm$ 1.0179) | -1.887 ( $\pm$ 0.9415) |  |  |

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Resting oxygen saturation level |
| Comparison groups                       | Placebo v VAY736                |
| Number of subjects included in analysis | 12                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.1269 <sup>[5]</sup>         |
| Method                                  | MMRM                            |
| Parameter estimate                      | Least Squares of the mean       |
| Point estimate                          | 1.77                            |
| Confidence interval                     |                                 |
| level                                   | Other: 80 %                     |
| sides                                   | 2-sided                         |
| lower limit                             | -0.219                          |
| upper limit                             | 3.759                           |
| Variability estimate                    | Standard error of the mean      |
| Dispersion value                        | 1.5422                          |

Notes:

[5] - 1-sided p-values were obtained using MMRM Model.

## Secondary: Number of participants with positive serum anti-VAY736 antibodies

|   |   |
|---|---|
| End point title   | Number of participants with positive serum anti-VAY736 antibodies |
| End point description:  |   |
| Number of participants with positive serum anti-VAY736 antibodies. A bridging ELISA method that is designed to detect the presence of anti-VAY736 antibodies in human serum was used. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Day 1, 29, 85, 169, 253 and 337   |   |

| End point values            | VAY736          | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 10              | 15              |  |  |
| Units: Participants         |                 |                 |  |  |
| Day 1                       | 1               | 3               |  |  |
| Day 29                      | 1               | 2               |  |  |
| Day 85                      | 1               | 1               |  |  |
| Day 169                     | 0               | 2               |  |  |
| Day 253                     | 2               | 1               |  |  |
| Day 337                     | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Ctrough of VAY736 from the serum concentration-time data

|                 |   |
|-----------------|---|
| End point title | Ctrough of VAY736 from the serum concentration-time data <sup>[6]</sup> |
|-----------------|---|

End point description:

At pre-dose on Day 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 and 337

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-dose on Day 1, 29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309 and 337

Notes:

[6] - 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: This endpoint is only applicable for VAY736 arm

| End point values                      | VAY736              |  |  |  |
|---------------------------------------|---------------------|--|--|--|
| Subject group type                    | Reporting group     |  |  |  |
| Number of subjects analysed           | 11                  |  |  |  |
| Units: nanogram (ng) / mililiter (mL) |                     |  |  |  |
| arithmetic mean (standard deviation)  |                     |  |  |  |
| Day 1                                 | 0.00 (± 0.00)       |  |  |  |
| Day 29                                | 676.79 (± 499.931)  |  |  |  |
| Day 57                                | 779.89 (± 645.363)  |  |  |  |
| Day 85                                | 786.63 (± 501.225)  |  |  |  |
| Day 113                               | 771.88 (± 623.268)  |  |  |  |
| Day 141                               | 1316.05 (± 877.240) |  |  |  |
| Day 169                               | 1019.00 (± 587.097) |  |  |  |
| Day 197                               | 985.50 (± 495.652)  |  |  |  |
| Day 225                               | 1271.10 (± 863.055) |  |  |  |
| Day 253                               | 998.57 (± 947.343)  |  |  |  |

|         |                         |  |  |  |
|---------|-------------------------|--|--|--|
| Day 281 | 705.00 ( $\pm$ 997.021) |  |  |  |
| Day 309 | 827.40 ( $\pm$ 678.836) |  |  |  |
| Day 337 | 688.50 ( $\pm$ 1172.12) |  |  |  |

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start up to end of study, assessed up to approximately 2.4 years

Adverse event reporting additional description:

Safety analyses were performed in the safety set including all participants who received at least one dose of any study drug

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | VAY736 |
|-----------------------|--------|

Reporting group description:

Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received 300 mg VAY736 administered subcutaneously every 4 weeks for 48 weeks on top of current standard-of-care therapy

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| Serious adverse events  | VAY736          | Placebo         | Total            |
|---|-----------------|-----------------|------------------|
| Total subjects affected by serious adverse events                   |                 |                 |                  |
| subjects affected / exposed   | 5 / 13 (38.46%) | 9 / 16 (56.25%) | 14 / 29 (48.28%) |
| number of deaths (all causes)                                       | 1               | 0               | 1                |
| number of deaths resulting from adverse events                      | 0               | 0               | 0                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                  |
| Basal cell carcinoma  |                 |                 |                  |
| subjects affected / exposed   | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)   |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0            |
| Prostate cancer   |                 |                 |                  |
| subjects affected / exposed   | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)   |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0           | 0 / 0            |
| Vascular disorders  |                 |                 |                  |
| Vasculitis  |                 |                 |                  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                |                |                |
| Aortic valve incompetence                       |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocardial infarction                           |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 1 / 16 (6.25%) | 2 / 29 (6.90%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                     |                |                |                |
| Vertigo   |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Eye disorders                                   |                |                |                |
| Retinal vein occlusion                          |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                |                |                |
| Pancreatitis                                    |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Hypoxia   |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Idiopathic pulmonary fibrosis                   |                |                |                |

|   |                |                 |                 |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 13 (7.69%) | 1 / 16 (6.25%)  | 2 / 29 (6.90%)  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0           | 0 / 1           |
| <b>Infections and infestations</b>              |                |                 |                 |
| Bronchitis                                      |                |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 3 / 16 (18.75%) | 3 / 29 (10.34%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>       |                |                 |                 |
| Dehydration                                     |                |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                                   | VAY736            | Placebo          | Total            |
|---|-------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events               |                   |                  |                  |
| subjects affected / exposed   | 13 / 13 (100.00%) | 15 / 16 (93.75%) | 28 / 29 (96.55%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                  |                  |
| Keratoacanthoma   |                   |                  |                  |
| subjects affected / exposed   | 1 / 13 (7.69%)    | 0 / 16 (0.00%)   | 1 / 29 (3.45%)   |
| occurrences (all)   | 1                 | 0                | 1                |
| Dysplastic naevus   |                   |                  |                  |
| subjects affected / exposed   | 0 / 13 (0.00%)    | 1 / 16 (6.25%)   | 1 / 29 (3.45%)   |
| occurrences (all)   | 0                 | 1                | 1                |
| Basal cell carcinoma  |                   |                  |                  |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)        | 1 / 13 (7.69%)<br>2 | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>2 |
| Vascular disorders                                      |                     |                     |                     |
| Hot flush   |                     |                     |                     |
| subjects affected / exposed                             | 2 / 13 (15.38%)     | 0 / 16 (0.00%)      | 2 / 29 (6.90%)      |
| occurrences (all)                                       | 2                   | 0                   | 2                   |
| Hypertension  |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 0 / 16 (0.00%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 1                   | 0                   | 1                   |
| General disorders and administration<br>site conditions |                     |                     |                     |
| Asthenia  |                     |                     |                     |
| subjects affected / exposed                             | 0 / 13 (0.00%)      | 1 / 16 (6.25%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 0                   | 1                   | 1                   |
| Chest discomfort  |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 0 / 16 (0.00%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 1                   | 0                   | 1                   |
| Chest pain  |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 0 / 16 (0.00%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 1                   | 0                   | 1                   |
| Fatigue   |                     |                     |                     |
| subjects affected / exposed                             | 2 / 13 (15.38%)     | 1 / 16 (6.25%)      | 3 / 29 (10.34%)     |
| occurrences (all)                                       | 2                   | 2                   | 4                   |
| Injection site bruising                                 |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 1 / 16 (6.25%)      | 2 / 29 (6.90%)      |
| occurrences (all)                                       | 1                   | 1                   | 2                   |
| Injection site dermatitis                               |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 0 / 16 (0.00%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 2                   | 0                   | 2                   |
| Injection site erythema                                 |                     |                     |                     |
| subjects affected / exposed                             | 2 / 13 (15.38%)     | 1 / 16 (6.25%)      | 3 / 29 (10.34%)     |
| occurrences (all)                                       | 2                   | 1                   | 3                   |
| Injection site inflammation                             |                     |                     |                     |
| subjects affected / exposed                             | 1 / 13 (7.69%)      | 0 / 16 (0.00%)      | 1 / 29 (3.45%)      |
| occurrences (all)                                       | 1                   | 0                   | 1                   |
| Injection site pain                                     |                     |                     |                     |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 0               | 1               | 1               |
| Injection site warmth                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 1               | 0               | 1               |
| Injection site rash                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 1               | 0               | 1               |
| Injection site pruritus                         |                 |                 |                 |
| subjects affected / exposed                     | 3 / 13 (23.08%) | 2 / 16 (12.50%) | 5 / 29 (17.24%) |
| occurrences (all)                               | 8               | 2               | 10              |
| Non-cardiac chest pain                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 0               | 1               | 1               |
| Immune system disorders                         |                 |                 |                 |
| Seasonal allergy                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 1               | 0               | 1               |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 1 / 16 (6.25%)  | 2 / 29 (6.90%)  |
| occurrences (all)                               | 1               | 1               | 2               |
| Dysphonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 0               | 1               | 1               |
| Cough   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 13 (23.08%) | 1 / 16 (6.25%)  | 4 / 29 (13.79%) |
| occurrences (all)                               | 3               | 1               | 4               |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                               | 0               | 1               | 1               |
| Idiopathic pulmonary fibrosis                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 13 (7.69%)  | 3 / 16 (18.75%) | 4 / 29 (13.79%) |
| occurrences (all)                               | 1               | 3               | 4               |
| Hypoxia   |                 |                 |                 |



|   |                      |                     |                      |
|---|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 13 (7.69%)<br>1  | 1 / 16 (6.25%)<br>1 | 2 / 29 (6.90%)<br>2  |
| Psychiatric disorders   |                      |                     |                      |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 13 (15.38%)<br>2 | 1 / 16 (6.25%)<br>1 | 3 / 29 (10.34%)<br>3 |
| Investigations  |                      |                     |                      |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)        | 2 / 13 (15.38%)<br>2 | 0 / 16 (0.00%)<br>0 | 2 / 29 (6.90%)<br>2  |
| Antinuclear antibody increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Blood creatine phosphokinase<br>decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Blood parathyroid hormone<br>decreased<br>subjects affected / exposed<br>occurrences (all)    | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Blood potassium increased<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Blood triglycerides increased   |                      |                     |                      |

|                                     |                 |                |                |
|-------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed         | 0 / 13 (0.00%)  | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 0               | 1              | 1              |
| Blood urea increased                |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Blood urine present                 |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Escherichia test positive           |                 |                |                |
| subjects affected / exposed         | 0 / 13 (0.00%)  | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 0               | 1              | 1              |
| Glucose urine present               |                 |                |                |
| subjects affected / exposed         | 0 / 13 (0.00%)  | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 0               | 1              | 1              |
| Gamma-glutamyltransferase increased |                 |                |                |
| subjects affected / exposed         | 2 / 13 (15.38%) | 0 / 16 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all)                   | 2               | 0              | 2              |
| Lymphocyte count decreased          |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Hepatic enzyme increased            |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Mean cell volume increased          |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Monocyte count increased            |                 |                |                |
| subjects affected / exposed         | 2 / 13 (15.38%) | 0 / 16 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all)                   | 2               | 0              | 2              |
| Neutrophil count increased          |                 |                |                |
| subjects affected / exposed         | 1 / 13 (7.69%)  | 0 / 16 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 1               | 0              | 1              |
| Protein urine present               |                 |                |                |
| subjects affected / exposed         | 0 / 13 (0.00%)  | 1 / 16 (6.25%) | 1 / 29 (3.45%) |
| occurrences (all)                   | 0               | 1              | 1              |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Urine albumin/creatinine ratio increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all)         | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 13 (7.69%)<br>1  | 4 / 16 (25.00%)<br>4 | 5 / 29 (17.24%)<br>5 |
| Urine analysis abnormal<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  |
| Urine protein/creatinine ratio increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1  | 1 / 16 (6.25%)<br>1  | 2 / 29 (6.90%)<br>2  |
| Injury, poisoning and procedural complications   |                      |                      |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 13 (7.69%)<br>1  | 1 / 16 (6.25%)<br>1  | 2 / 29 (6.90%)<br>2  |
| Facial bones fracture<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  |
| Heat stroke<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Injection related reaction<br>subjects affected / exposed<br>occurrences (all)               | 2 / 13 (15.38%)<br>4 | 0 / 16 (0.00%)<br>0  | 2 / 29 (6.90%)<br>4  |
| Sunburn<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 13 (0.00%)<br>0  | 2 / 16 (12.50%)<br>2 | 2 / 29 (6.90%)<br>2  |
| Cardiac disorders  |                      |                      |                      |
| Aortic valve incompetence<br>subjects affected / exposed<br>occurrences (all)                | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Arteriosclerosis coronary artery<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Nervous system disorders   |                      |                      |                      |
| Cognitive disorder<br>subjects affected / exposed<br>occurrences (all)               | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Cervical radiculopathy<br>subjects affected / exposed<br>occurrences (all)           | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 13 (15.38%)<br>3 | 2 / 16 (12.50%)<br>2 | 4 / 29 (13.79%)<br>5 |
| Carotid artery stenosis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1  |
| Memory impairment<br>subjects affected / exposed<br>occurrences (all)                | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1  |
| Blood and lymphatic system disorders   |                      |                      |                      |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| Eosinophilia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Ear and labyrinth disorders<br>Eustachian tube dysfunction<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Corneal degeneration<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 13 (7.69%)<br>1  | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 13 (0.00%)<br>0  | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 3 / 13 (23.08%)<br>3 | 1 / 16 (6.25%)<br>1 | 4 / 29 (13.79%)<br>4 |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 13 (15.38%)<br>2 | 0 / 16 (0.00%)<br>0 | 2 / 29 (6.90%)<br>2  |
| Enteritis  |                      |                     |                      |

|  |                |                 |                 |
|--|----------------|-----------------|-----------------|
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 1              | 0               | 1               |
| Flatulence                             |                |                 |                 |
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 1              | 0               | 1               |
| Frequent bowel movements               |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Nausea                                 |                |                 |                 |
| subjects affected / exposed            | 1 / 13 (7.69%) | 2 / 16 (12.50%) | 3 / 29 (10.34%) |
| occurrences (all)                      | 1              | 3               | 4               |
| Vomiting                               |                |                 |                 |
| subjects affected / exposed            | 1 / 13 (7.69%) | 2 / 16 (12.50%) | 3 / 29 (10.34%) |
| occurrences (all)                      | 1              | 2               | 3               |
| Skin and subcutaneous tissue disorders |                |                 |                 |
| Alopecia                               |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Dermatitis atopic                      |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Drug eruption                          |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Hyperhidrosis                          |                |                 |                 |
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 1              | 0               | 1               |
| Keloid scar                            |                |                 |                 |
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 1              | 0               | 1               |
| Photosensitivity reaction              |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 1               | 1               |
| Pruritus                               |                |                 |                 |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                      | 0              | 2               | 2               |

|  |                     |                      |                     |
|--|---------------------|----------------------|---------------------|
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)    | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 13 (0.00%)<br>0 | 2 / 16 (12.50%)<br>3 | 2 / 29 (6.90%)<br>3 |
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)          | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1 |
| Renal and urinary disorders  |                     |                      |                     |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1 |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)           | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Musculoskeletal and connective tissue disorders                          |                     |                      |                     |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0  | 1 / 29 (3.45%)<br>1 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Limb discomfort<br>subjects affected / exposed<br>occurrences (all)      | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)        | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1  | 1 / 29 (3.45%)<br>1 |
| Osteoporosis   |                     |                      |                     |

|                                   |                 |                 |                 |
|-----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed       | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 0               | 1               | 1               |
| Musculoskeletal pain              |                 |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 1               | 0               | 1               |
| Pain in extremity                 |                 |                 |                 |
| subjects affected / exposed       | 2 / 13 (15.38%) | 0 / 16 (0.00%)  | 2 / 29 (6.90%)  |
| occurrences (all)                 | 2               | 0               | 2               |
| Infections and infestations       |                 |                 |                 |
| Bronchitis                        |                 |                 |                 |
| subjects affected / exposed       | 2 / 13 (15.38%) | 2 / 16 (12.50%) | 4 / 29 (13.79%) |
| occurrences (all)                 | 2               | 3               | 5               |
| Conjunctivitis                    |                 |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 0               | 1               | 1               |
| Respiratory tract infection       |                 |                 |                 |
| subjects affected / exposed       | 2 / 13 (15.38%) | 1 / 16 (6.25%)  | 3 / 29 (10.34%) |
| occurrences (all)                 | 2               | 1               | 3               |
| Lower respiratory tract infection |                 |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%)  | 1 / 16 (6.25%)  | 2 / 29 (6.90%)  |
| occurrences (all)                 | 2               | 1               | 3               |
| Influenza                         |                 |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%)  | 0 / 16 (0.00%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 1               | 0               | 1               |
| Rhinitis                          |                 |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 0               | 1               | 1               |
| Tooth infection                   |                 |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 0               | 1               | 1               |
| Upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed       | 2 / 13 (15.38%) | 2 / 16 (12.50%) | 4 / 29 (13.79%) |
| occurrences (all)                 | 5               | 2               | 7               |
| Urinary tract infection           |                 |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%)  | 1 / 16 (6.25%)  | 1 / 29 (3.45%)  |
| occurrences (all)                 | 0               | 2               | 2               |



|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 13 (7.69%)<br>1 | 1 / 16 (6.25%)<br>1 | 2 / 29 (6.90%)<br>2 |
| Metabolism and nutrition disorders  |                     |                     |                     |
| Vitamin D deficiency<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1 |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 13 (7.69%)<br>1 | 0 / 16 (0.00%)<br>0 | 1 / 29 (3.45%)<br>1 |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 13 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 1 / 29 (3.45%)<br>1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 30 August 2017   | This amendment corrected an inconsistency within the protocol around the potential need to follow-up partners of patients who could become pregnant during the study. At the time of this amendment, there were no patients enrolled   |
| 23 October 2017  | This amendment clarified that the St. George's Respiratory Questionnaire in IPF (SGRQ-I) was not available for use in all study countries planned in this study.   |
| 08 December 2017 | This amendment addressed questions from MHRA upon their initial review of the study protocol.  |
| 27 February 2018 | This amendment addressed questions from the Irish and French Health Authorities upon their initial reviews of the study protocol. In addition, the baseline visit was removed in order to reduce patient burden, as similar assessments were scheduled to be captured during Treatment Epoch Day 1 |
| 03 December 2018 | This amendment corrected an error in the definition of a serious adverse event (SAE). The bullet formatting was corrected, and missing text was added to clarify when inpatient hospitalization or prolongation of an existing hospitalization was considered a SAE.                               |
| 10 July 2019     | The purpose of this amendment was to: (a) adjust the sample size and timing of the IA to align with clinical development strategy (b) reduce protocol complexity and (c) implement other minor updates throughout the protocol for clarity.  |
| 27 March 2020    | This amendment revised the eligibility criteria with the aim of accelerating enrollment  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, data using 9999 as data points in this record are not an accurate representation of the results. Moreover, disposition in PK and PD/safety Follow-up Epochs could not be added. Please use <https://www.novctrd.com>

Notes: