



## Clinical trial results:

### A Phase IIa, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety and Efficacy of 28 Day Oral Administration of BAY 85-8501 in Patients with non-Cystic Fibrosis Bronchiectasis

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004491-18 |
| Trial protocol           | GB ES IT       |
| Global end of trial date | 13 June 2014   |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 12 July 2016 |
| First version publication date | 24 July 2015 |

#### Trial information

##### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | BAY85-8501 / 16359 |
|-----------------------|--------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01818544 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bayer HealthCare AG   |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368                                      |
| Public contact               | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com |
| Scientific contact           | Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.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                       | 22 September 2014 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 13 June 2014      |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 28 day oral administration of BAY 85-8501 versus placebo in subjects with non-Cystic Fibrosis (CF) Bronchiectasis (BE).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 22 April 2013 |
| Long term follow-up planned                               | Yes           |
| Long term follow-up rationale                             | Safety        |
| Long term follow-up duration                              | 1 Months      |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Germany: 13       |
| Country: Number of subjects enrolled | Spain: 18         |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Italy: 54         |
| Worldwide total number of subjects   | 94                |
| EEA total number of subjects         | 94                |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 29 |
| From 65 to 84 years       | 65 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 27 sites in 4 countries between 22 April 2013 (first subject first visit) and 13 June 2014 (last subject last visit).

### Pre-assignment

Screening details:

Of 139 subjects screened, 94 subjects were randomized to the study. The reason for 45 screen failures was non-fulfilment of the inclusion or exclusion and subject withdrawal criteria.

### 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, Carer, Assessor |

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | BAY85-8501 |

Arm description:

Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | BAY85-8501   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Daily oral dose of 1 mg BAY85-8501 tablets for 28 days.

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

Arm description:

Placebo matched to BAY85-8501 for 28 days.

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

Dosage and administration details:

Placebo matched to BAY85-8501 for 28 days.

| <b>Number of subjects in period 1</b> | BAY85-8501 | Placebo |
|---------------------------------------|------------|---------|
| Started                               | 47         | 47      |
| Treated                               | 45         | 47      |
| Completed                             | 37         | 45      |
| Not completed                         | 10         | 2       |
| Consent withdrawn by subject          | 1          | -       |
| Protocol violation                    | 2          | -       |
| Adverse event                         | 6          | 1       |
| Unspecified                           | 1          | -       |
| Lost to follow-up                     | -          | 1       |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | BAY85-8501 |
|-----------------------|------------|

Reporting group description:

Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.

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

Reporting group description:

Placebo matched to BAY85-8501 for 28 days.

| Reporting group values  | BAY85-8501      | Placebo        | Total |
|---|-----------------|----------------|-------|
| Number of subjects  | 47              | 47             | 94    |
| Age categorical<br>Units: Subjects                                      |                 |                |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 64.1<br>± 12.21 | 68.6<br>± 8.04 | -     |
| Gender categorical<br>Units: Subjects                                   |                 |                |       |
| Female  | 22              | 22             | 44    |
| Male  | 25              | 25             | 50    |

## End points

### End points reporting groups

|  |                                    |
|--|------------------------------------|
| Reporting group title  | BAY85-8501                         |
| Reporting group description:<br>Daily oral dose of 1 milligram (mg) BAY85-8501 tablets for 28 days.  |                                    |
| Reporting group title  | Placebo                            |
| Reporting group description:<br>Placebo matched to BAY85-8501 for 28 days.   |                                    |
| Subject analysis set title   | Safety Population                  |
| Subject analysis set type  | Safety analysis                    |
| Subject analysis set description:<br>Safety population (N= 92) was defined as all subjects who received at least one dose of study medication. |                                    |
| Subject analysis set title   | Full Analysis Set (FAS) Population |
| Subject analysis set type  | Full analysis                      |
| Subject analysis set description:<br>FAS population (N= 94) was defined as all randomized subjects.  |                                    |

### Primary: Number Of Subjects Who Need To Discontinue Study Medication Due To Findings In Physical Examination

|   |  |
|---|--|
| End point title   | Number Of Subjects Who Need To Discontinue Study Medication Due To Findings In Physical Examination <sup>[1]</sup> |
| End point description:  |  |
| End point type  | Primary  |
| End point timeframe:<br>From start of study treatment up to follow-up visit (28 days after last dose) |  |

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values            | BAY85-8501        | Placebo           |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 45 <sup>[2]</sup> | 47 <sup>[3]</sup> |  |  |
| Units: Subjects             | 4                 | 1                 |  |  |

Notes:

[2] - Safety population

[3] - Safety population

### Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Systolic Blood Pressure At Days 7, 14, 21, 28, 56

|   |  |
|---|--|
| End point title   | Change From Baseline in Systolic Blood Pressure At Days 7, 14, 21, 28, 56 <sup>[4]</sup> |
| End point description:<br>In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |  |
| End point type  | Primary  |

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[4] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | BAY85-8501        | Placebo           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 45 <sup>[5]</sup> | 47 <sup>[6]</sup> |  |  |
| Units: millimeter of mercury         |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Baseline (N= 45, 47)                 | 134.6 (± 21.48)   | 133.1 (± 16.94)   |  |  |
| Change at Day 7 (N= 43, 47)          | 1.1 (± 13.75)     | 0.8 (± 12.68)     |  |  |
| Change at Day 14 (N= 42, 46)         | -1.4 (± 14.64)    | -1.1 (± 14.34)    |  |  |
| Change at Day 21 (N= 42, 47)         | -3.4 (± 15.93)    | -1 (± 13.03)      |  |  |
| Change at Day 28 (N= 44, 47)         | -3.6 (± 13.13)    | -2.9 (± 16.21)    |  |  |
| Change at Day 56 (N= 39, 46)         | -3 (± 15.37)      | -2 (± 13.17)      |  |  |

Notes:

[5] - Safety population

[6] - Safety population

## Statistical analyses

No statistical analyses for this end point

## Primary: Change From Baseline in Diastolic Blood Pressure At Days 7, 14, 21, 28, 56

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Diastolic Blood Pressure At Days 7, 14, 21, 28, 56 <sup>[7]</sup> |
|-----------------|---|

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | BAY85-8501        | Placebo           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 45 <sup>[8]</sup> | 47 <sup>[9]</sup> |  |  |
| Units: millimeter of mercury         |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Baseline (N= 45, 47)                 | 76.9 (± 10.81)    | 77.3 (± 11.32)    |  |  |
| Change at Day 7 (N= 43, 47)          | -0.7 (± 8.39)     | -3.6 (± 9.29)     |  |  |
| Change at Day 14 (N= 42, 46)         | -2.4 (± 10.19)    | -2.3 (± 8.67)     |  |  |
| Change at Day 21 (N= 42, 47)         | -1.1 (± 8.43)     | -2 (± 9.14)       |  |  |
| Change at Day 28 (N= 44, 47)         | -2 (± 7.99)       | -3.7 (± 9.43)     |  |  |
| Change at Day 56 (N= 39, 46)         | -2.5 (± 9.67)     | -3.8 (± 8.97)     |  |  |



Notes:

[8] - Safety population

[9] - Safety population

## Statistical analyses

No statistical analyses for this end point

### Primary: Change From Baseline in Heart Rate At Days 7, 14, 21, 28, 56

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Heart Rate At Days 7, 14, 21, 28, |
|-----------------|---|

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 45 <sup>[11]</sup> | 47 <sup>[12]</sup> |  |  |
| Units: beats per minute              |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 45, 47)                 | 74.6 (± 10.82)     | 74.5 (± 10.6)      |  |  |
| Change at Day 7 (N= 43, 47)          | 0.5 (± 9.35)       | -0.4 (± 11.06)     |  |  |
| Change at Day 14 (N= 42, 46)         | -2.2 (± 8.28)      | 0.2 (± 9.5)        |  |  |
| Change at Day 21 (N= 42, 47)         | 0.2 (± 10.93)      | 1.5 (± 10.96)      |  |  |
| Change at Day 28 (N= 44, 47)         | -0.7 (± 10.09)     | 1 (± 10.8)         |  |  |
| Change at Day 56 (N= 39, 46)         | -1.9 (± 12.46)     | 1.7 (± 8.57)       |  |  |

Notes:

[11] - Safety population

[12] - Safety population

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With new Abnormal (Pathologic) Electrocardiogram (ECG) Findings From Baseline to Day 28

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With new Abnormal (Pathologic) Electrocardiogram (ECG) Findings From Baseline to Day 28 <sup>[13]</sup> |
|-----------------|--|

End point description:

ECG abnormalities that were considered clinically significant (CS) or clinically insignificant (CI) by the investigator were reported. Parameters analyzed included ventricular rate, PR duration, QRS duration, and QT duration to the subjects.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28

Notes:

[13] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values               | BAY85-8501         | Placebo            |  |  |
|--------------------------------|--------------------|--------------------|--|--|
| Subject group type             | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed    | 45 <sup>[14]</sup> | 47 <sup>[15]</sup> |  |  |
| Units: Subjects                |                    |                    |  |  |
| Baseline: Abnormal, CI         | 6                  | 14                 |  |  |
| Baseline: Abnormal, CS         | 0                  | 0                  |  |  |
| Change at Day 7: Abnormal, CI  | 4                  | 12                 |  |  |
| Change at Day 7: Abnormal, CS  | 0                  | 0                  |  |  |
| Change at Day 14: Abnormal, CI | 6                  | 16                 |  |  |
| Change at Day 14: Abnormal, CS | 0                  | 1                  |  |  |
| Change at Day 21: Abnormal, CI | 5                  | 14                 |  |  |
| Change at Day 21: Abnormal, CS | 0                  | 0                  |  |  |
| Change at Day 28: Abnormal, CI | 7                  | 13                 |  |  |
| Change at Day 28: Abnormal, CS | 0                  | 0                  |  |  |

Notes:

[14] - Safety population

[15] - Safety population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects who Show Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TB) Abnormalities in Their Safety Lab Assessment

|                 |   |
|-----------------|---|
| End point title | Number of Subjects who Show Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TB) Abnormalities in Their Safety Lab Assessment <sup>[16]</sup> |
|-----------------|---|

End point description:

The pre-specified laboratory abnormalities included ALT and AST greater than or equal to ( $\geq$ ) 3 times upper limit of normal (ULN) and total bilirubin with an increase of 200% from baseline.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[16] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values            | BAY85-8501         | Placebo            |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 45 <sup>[17]</sup> | 45 <sup>[18]</sup> |  |  |
| Units: Subjects             |                    |                    |  |  |
| Baseline (ALT)              | 1                  | 0                  |  |  |
| Change at Day 7 (ALT)       | 0                  | 0                  |  |  |
| Change at Day 14 (ALT)      | 0                  | 0                  |  |  |
| Change at Day 21 (ALT)      | 0                  | 0                  |  |  |
| Change at Day 28 (ALT)      | 0                  | 1                  |  |  |

|                        |   |   |  |  |
|------------------------|---|---|--|--|
| Change at Day 56 (ALT) | 0 | 0 |  |  |
| Baseline (AST)         | 0 | 0 |  |  |
| Change at Day 7 (AST)  | 0 | 1 |  |  |
| Change at Day 14 (AST) | 0 | 0 |  |  |
| Change at Day 21 (AST) | 0 | 0 |  |  |
| Change at Day 28 (AST) | 0 | 0 |  |  |
| Change at Day 56 (AST) | 0 | 0 |  |  |
| Change at Day 7 (TB)   | 0 | 1 |  |  |
| Change at Day 14 (TB)  | 0 | 0 |  |  |
| Change at Day 21 (TB)  | 1 | 0 |  |  |
| Change at Day 28 (TB)  | 0 | 1 |  |  |
| Change at Day 56 (TB)  | 0 | 0 |  |  |

Notes:

[17] - Safety Population

[18] - Safety population

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With Drug-Related Adverse Events as a Measure of Safety And Tolerability

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Drug-Related Adverse Events as a Measure of Safety And Tolerability <sup>[19]</sup> |
|-----------------|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent adverse events were defined as adverse events/serious adverse events that started or worsened after the start of study drug administration.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

Notes:

[19] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values                    | BAY85-8501         | Placebo            |  |  |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed         | 45 <sup>[20]</sup> | 47 <sup>[21]</sup> |  |  |
| Units: Subjects                     |                    |                    |  |  |
| Any Study Drug Related TEAE         | 11                 | 12                 |  |  |
| Any Study Drug Related Serious TEAE | 0                  | 0                  |  |  |

Notes:

[20] - Safety population

[21] - Safety population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Pulmonary Function Test Forced Expired

**Volume in 1 Second (FEV1) At Days 7, 14, 21, 28, 56**

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Pulmonary Function Test Forced Expired Volume in 1 Second (FEV1) At Days 7, 14, 21, 28, 56 |
|-----------------|--|

End point description:

FEV1 is a pulmonary function test, defined as the amount of air expelled in 1 second, included pre-bronchodilator (BD) and post-bronchodilator (BD) tests. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

| End point values                             | BAY85-8501         | Placebo            |  |  |
|--|--------------------|--------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed                  | 47 <sup>[22]</sup> | 47 <sup>[23]</sup> |  |  |
| Units: liters                                |                    |                    |  |  |
| arithmetic mean (standard deviation)         |                    |                    |  |  |
| Baseline Pre-bronchodilator (BD) (N= 39, 44) | 1.631 (± 0.6687)   | 1.448 (± 0.4387)   |  |  |
| Baseline Post-BD (N= 44, 47)                 | 1.705 (± 0.5875)   | 1.522 (± 0.4489)   |  |  |
| Change at Day 7: Pre-BD (N= 37, 44)          | -0.01 (± 0.1331)   | -0.007 (± 0.1153)  |  |  |
| Change at Day 7: Post-BD (N= 43, 47)         | 0.01 (± 0.1526)    | 0.004 (± 0.1343)   |  |  |
| Change at Day 14: Pre-BD (N= 36, 43)         | 0.018 (± 0.1617)   | -0.03 (± 0.1528)   |  |  |
| Change at Day 14: Post-BD (N= 42, 46)        | 0.035 (± 0.1698)   | -0.028 (± 0.1798)  |  |  |
| Change at Day 21: Pre-BD (N= 36, 44)         | -0.024 (± 0.1534)  | -0.075 (± 0.156)   |  |  |
| Change at Day 21: Post-BD (N= 42, 47)        | 0.016 (± 0.137)    | -0.032 (± 0.1637)  |  |  |
| Change at Day 28: Pre-BD (N= 37, 44)         | -0.004 (± 0.1552)  | -0.078 (± 0.1986)  |  |  |
| Change at Day 28: Post-BD (N= 42, 47)        | 0.026 (± 0.1924)   | -0.051 (± 0.197)   |  |  |
| Change at Day 56: Pre-BD (N= 34, 43)         | -0.014 (± 0.1541)  | -0.063 (± 0.2214)  |  |  |
| Change at Day 56: Post-BD (N= 39, 45)        | -0.026 (± 0.174)   | -0.073 (± 0.2101)  |  |  |

Notes:

[22] - FAS population

[23] - FAS population

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

FEV1 was analyzed by an analysis of covariance (ANCOVA) with baseline as a covariate and treatment as a factor. Adjusted means (least square [LS] means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | BAY85-8501 v Placebo |
|-------------------|----------------------|

|   |                    |
|---|--------------------|
| Number of subjects included in analysis | 94                 |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | other              |
| P-value                                 | = 0.0558           |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS-mean Difference |
| Point estimate                          | 0.082              |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | -0.0021            |
| upper limit                             | 0.1653             |

### Secondary: Change From Baseline in Pulmonary Function Test Forced Vital Capacity (FVC) at Days 7, 14, 21, 28, 56

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Pulmonary Function Test Forced Vital Capacity (FVC) at Days 7, 14, 21, 28, 56 |
|-----------------|---|

End point description:

FVC is defined as the total amount of air exhaled during the lung function test. FVC is a pulmonary function test included pre-bronchodilator and post-bronchodilator tests. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 7, 14, 21, 28, 56

| End point values                      | BAY85-8501         | Placebo            |  |  |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed           | 47 <sup>[24]</sup> | 47 <sup>[25]</sup> |  |  |
| Units: liters                         |                    |                    |  |  |
| arithmetic mean (standard deviation)  |                    |                    |  |  |
| Baseline Pre-BD (N= 39, 44)           | 2.733 (± 1.0127)   | 2.46 (± 0.7168)    |  |  |
| Baseline Post-BD (N= 44, 47)          | 2.819 (± 0.9748)   | 2.529 (± 0.673)    |  |  |
| Change at Day 7: Pre-BD (N= 37, 44)   | 0.008 (± 0.2387)   | -0.003 (± 0.2294)  |  |  |
| Change at Day 7: Post-BD (N= 43, 47)  | 0.031 (± 0.2422)   | 0.007 (± 0.2397)   |  |  |
| Change at Day 14: Pre-BD (N= 36, 43)  | 0.026 (± 0.2193)   | -0.044 (± 0.2678)  |  |  |
| Change at Day 14: Post-BD (N= 42, 46) | 0.072 (± 0.257)    | 0 (± 0.1924)       |  |  |
| Change at Day 21: Pre-BD (N= 36, 44)  | -0.01 (± 0.2658)   | -0.073 (± 0.2227)  |  |  |
| Change at Day 21: Post-BD (N= 42, 47) | 0.077 (± 0.2832)   | -0.031 (± 0.2377)  |  |  |
| Change at Day 28: Pre-BD (N= 37, 44)  | -0.009 (± 0.2997)  | -0.06 (± 0.2495)   |  |  |

|                                       |                  |                   |  |  |
|---------------------------------------|------------------|-------------------|--|--|
| Change at Day 28: Post-BD (N= 42, 47) | 0.013 (± 0.3402) | -0.029 (± 0.2086) |  |  |
| Change at Day 56: Pre-BD (N= 34, 43)  | -0.04 (± 0.2676) | -0.04 (± 0.3101)  |  |  |
| Change at Day 56: Post-BD (N= 39, 45) | 0.007 (± 0.3405) | -0.03 (± 0.2734)  |  |  |

Notes:

[24] - FAS population

[25] - FAS population

## Statistical analyses

| Statistical analysis title   | Statistical analysis 1 |
|--|------------------------|
| Statistical analysis description:  |                        |
| FVC was analyzed by an ANCOVA with baseline as a covariate and treatment as a factor. Adjusted means (LS means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated. |                        |
| Comparison groups  | BAY85-8501 v Placebo   |
| Number of subjects included in analysis  | 94                     |
| Analysis specification   | Pre-specified          |
| Analysis type  | other                  |
| P-value  | = 0.3993               |
| Method   | ANCOVA                 |
| Parameter estimate   | LS-mean Difference     |
| Point estimate   | 0.051                  |
| Confidence interval  |                        |
| level  | 95 %                   |
| sides  | 2-sided                |
| lower limit  | -0.0686                |
| upper limit  | 0.1704                 |

## Secondary: Change From Baseline in Pulmonary Function Test Forced Expiratory Flow Over the Middle Half of Subject's Forced Vital Capacity (FVC) (FEF25-75) at Days 7, 14, 21, 28, 56

|   |   |
|---|---|
| End point title   | Change From Baseline in Pulmonary Function Test Forced Expiratory Flow Over the Middle Half of Subject's Forced Vital Capacity (FVC) (FEF25-75) at Days 7, 14, 21, 28, 56 |
| End point description:  |   |
| FEF 25 Percent (%) - 75% measurement describes the amount of air expelled from the lungs during the middle half (25% - 75%) of the forced vital capacity test. FEF25-75 is a pulmonary function test included pre-BD and post-BDs. The pre-BDs were performed prior to administration of any BD where as post-BDs were obtained within at least 15 minutes and no more than 30 minutes after administration of standard dose of BD. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Baseline (Day 1), Day 7, 14, 21, 28, 56   |   |

| End point values                      | BAY85-8501         | Placebo            |  |  |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed           | 47 <sup>[26]</sup> | 47 <sup>[27]</sup> |  |  |
| Units: liter per second               |                    |                    |  |  |
| arithmetic mean (standard deviation)  |                    |                    |  |  |
| Baseline: Pre-BD (N= 37, 43)          | 0.927 (± 0.7019)   | 0.79 (± 0.4473)    |  |  |
| Baseline: Post-BD (N= 41, 46)         | 0.96 (± 0.6376)    | 0.858 (± 0.4768)   |  |  |
| Change at Day 7: Pre-BD (N= 35, 43)   | -0.021 (± 0.1989)  | -0.033 (± 0.1622)  |  |  |
| Change at Day 7: Post-BD (N= 40, 46)  | 0.045 (± 0.3017)   | -0.004 (± 0.2318)  |  |  |
| Change at Day 14: Pre-BD (N= 34, 42)  | 0.028 (± 0.3661)   | -0.03 (± 0.2288)   |  |  |
| Change at Day 14: Post-BD (N= 39, 45) | 0.064 (± 0.4494)   | -0.023 (± 0.3312)  |  |  |
| Change at Day 21: Pre-BD (N= 34, 43)  | -0.019 (± 0.2114)  | -0.088 (± 0.2813)  |  |  |
| Change at Day 21: Post-BD (N= 39, 46) | -0.058 (± 0.3483)  | -0.06 (± 0.2851)   |  |  |
| Change at Day 28: Pre-BD (N= 35, 43)  | -0.045 (± 0.3533)  | -0.103 (± 0.3242)  |  |  |
| Change at Day 28: Post-BD (N= 39, 46) | 0.081 (± 0.4294)   | -0.038 (± 0.3975)  |  |  |
| Change at Day 56: Pre-BD (N= 32, 42)  | 0.07 (± 0.3323)    | -0.068 (± 0.3002)  |  |  |
| Change at Day 56: Post-BD (N= 36, 44) | -0.066 (± 0.5485)  | -0.077 (± 0.4097)  |  |  |

Notes:

[26] - FAS population

[27] - FAS population

## Statistical analyses

| Statistical analysis title  | Statistical analysis 1 |
|---|------------------------|
| Statistical analysis description:   |                        |
| FEF25-75 was analyzed by an ANCOVA with baseline as a covariate and treatment as a factor. Adjusted means (LS means) for treatment, as well as the difference in LS means between treatment groups, and the corresponding 95% confidence intervals were calculated. |                        |
| Comparison groups   | BAY85-8501 v Placebo   |
| Number of subjects included in analysis   | 94                     |
| Analysis specification  | Pre-specified          |
| Analysis type   | other                  |
| P-value   | = 0.1159               |
| Method  | ANCOVA                 |
| Parameter estimate  | LS-mean Difference     |
| Point estimate  | 0.138                  |
| Confidence interval   |                        |
| level   | 95 %                   |
| sides   | 2-sided                |
| lower limit   | -0.0348                |
| upper limit   | 0.3114                 |

## Secondary: Change From Baseline in Total Score on St. George's Respiratory Questionnaire (SGRQ) at Day 28 and 56

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Total Score on St. George's Respiratory Questionnaire (SGRQ) at Day 28 and 56 |
|-----------------|---|

End point description:

SGRQ has been developed to measure the impact of respiratory disease on health status. The SGRQ scoring was done 0-100% with 0 being no impairment of quality of life. This was scored separately for each of 3 sections (Activity, Impact and Symptom) of the questionnaire and a summary score utilizing responses to all items was the total SGRQ score. This total score ranged from zero to 100%. Score range of change from baseline between -4 to +4 points indicate "no clinical relevant change"; less than (<) 4 points indicate "improvement"; greater than (>) 4 points indicate "deterioration". In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 28 and 56

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[28]</sup> | 47 <sup>[29]</sup> |  |  |
| Units: scores on a scale             |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 42, 46)                 | 43.18 (± 20.159)   | 39.68 (± 14.546)   |  |  |
| Change at Day 28 (N= 40, 45)         | 0.36 (± 9.051)     | 0.18 (± 11.715)    |  |  |
| Change at Day 56 (N= 36, 44)         | -0.87 (± 6.851)    | 1.54 (± 10.874)    |  |  |

Notes:

[28] - FAS population

[29] - FAS population

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Baseline value was defined as the last non-missing assessment prior to the first dose of study drug. Adjusted means was defined as LS means. Data at the EOT (Week 4/Day 28) visit analyzed by the ANCOVA with baseline as a covariate and treatment as a factor (BAY85-8501 versus placebo).

|   |                      |
|---|----------------------|
| Comparison groups                       | BAY85-8501 v Placebo |
| Number of subjects included in analysis | 94                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other                |
| P-value                                 | = 0.7028             |
| Method                                  | ANCOVA               |
| Parameter estimate                      | LS-mean Difference   |
| Point estimate                          | 0.862                |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -3.6172              |
| upper limit                             | 5.3412               |



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**Secondary: Change From Baseline in 24 Hours Sputum Weight at Day 28**

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|                 |  |
|-----------------|--|
| End point title | Change From Baseline in 24 Hours Sputum Weight at Day 28 |
|-----------------|--|

End point description:

In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 28

---

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[30]</sup> | 47 <sup>[31]</sup> |  |  |
| Units: gram(s)                       |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 45, 47)                 | 22.14 (± 19.8151)  | 25.431 (± 24.4686) |  |  |
| Change at Day 28 (N= 40, 44)         | -0.126 (± 14.3549) | -3.398 (± 11.4987) |  |  |

Notes:

[30] - FAS population

[31] - FAS population

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Alpha-1 Antitrypsin Human Neutrophil Elastase (A1AH-NE) Complex, Interleukin-8 (IL-8)**

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|                 |  |
|-----------------|--|
| End point title | Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Alpha-1 Antitrypsin Human Neutrophil Elastase (A1AH-NE) Complex, Interleukin-8 (IL-8) |
|-----------------|--|

End point description:

Sputum biomarker assessments were taken from induced sputum. Inflammatory markers, included IL-8, A1AH-NE complex were recorded. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

---

| End point values                      | BAY85-8501         | Placebo            |  |  |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed           | 47 <sup>[32]</sup> | 47 <sup>[33]</sup> |  |  |
| Units: microgram per liter            |                    |                    |  |  |
| arithmetic mean (standard deviation)  |                    |                    |  |  |
| Baseline: A1AH-NE (N= 44, 47)         | 22.558 (± 19.408)  | 23 (± 37.4346)     |  |  |
| Change at Day 14: A1AH-NE (N= 38, 45) | 0.62 (± 13.338)    | 13.482 (± 62.8838) |  |  |
| Change at Day 28: A1AH-NE (N= 40, 45) | -4.805 (± 17.3091) | -1.803 (± 24.2774) |  |  |
| Change at Day 56: A1AH-NE (N= 34, 42) | -1.985 (± 17.5933) | 10.17 (± 43.4871)  |  |  |
| Baseline: IL-8 (N= 44, 47)            | 105.5 (± 112.305)  | 95.7 (± 91.279)    |  |  |
| Change at Day 14: IL-8 (N= 38, 45)    | 9.19 (± 59.909)    | -6.73 (± 52.883)   |  |  |
| Change at Day 28: IL-8 (N= 40, 46)    | 13.14 (± 58.059)   | -12.19 (± 51.165)  |  |  |
| Change at Day 56: IL-8 (N= 34, 42)    | 20.66 (± 62.955)   | -1.42 (± 73.201)   |  |  |

Notes:

[32] - FAS population

[33] - FAS population

## Statistical analyses

| Statistical analysis title              | Alpha-1-antitrypsin Human NE Complex in Sputum |
|---|--|
| Comparison groups                       | BAY85-8501 v Placebo                           |
| Number of subjects included in analysis | 94   |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | other  |
| P-value                                 | = 0.311  |
| Method                                  | ANCOVA   |
| Parameter estimate                      | LS-mean Difference                             |
| Point estimate                          | -2.87  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -8.475   |
| upper limit                             | 2.732  |

| Statistical analysis title              | Interleukin-8 in Sputum |
|---|-------------------------|
| Comparison groups                       | BAY85-8501 v Placebo    |
| Number of subjects included in analysis | 94                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.0215                |
| Method                                  | ANCOVA                  |
| Parameter estimate                      | LS-mean Difference      |
| Point estimate                          | 27.06                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 4.093   |
| upper limit         | 50.021  |

## Secondary: Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Neutrophil cell Count

|                 |  |
|-----------------|--|
| End point title | Change From Baseline of Biomarkers in Sputum at Days 14, 28, 56: Neutrophil cell Count |
|-----------------|--|

End point description:

Sputum biomarker assessments were taken from induced sputum. Inflammatory markers, included neutrophil cell count. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[34]</sup> | 47 <sup>[35]</sup> |  |  |
| Units: giga per liter                |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 41, 39)                 | 17.76 (± 21.3226)  | 20.107 (± 25.2439) |  |  |
| Change at Day 14 (N= 32, 34)         | -0.301 (± 17.1693) | -0.11 (± 16.0611)  |  |  |
| Change at Day 28 (N= 36, 36)         | -3.446 (± 12.6294) | 0.786 (± 27.9962)  |  |  |
| Change at Day 56 (N= 25, 34)         | -0.513 (± 12.5183) | -2.067 (± 23.12)   |  |  |

Notes:

[34] - FAS population

[35] - FAS population

## Statistical analyses

|   |                                 |
|---|---------------------------------|
| Statistical analysis title              | Neutrophil cell Count in Sputum |
| Comparison groups                       | BAY85-8501 v Placebo            |
| Number of subjects included in analysis | 94                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.3704                        |
| Method                                  | ANCOVA                          |
| Parameter estimate                      | LS-mean Difference              |
| Point estimate                          | -4.5                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -14.463 |
| upper limit         | 5.46    |

### Secondary: Change From Baseline of Human Neutrophil Elastase (NE) Activity in Sputum at Days 14, 28, 56

|   |  |
|---|--|
| End point title   | Change From Baseline of Human Neutrophil Elastase (NE) Activity in Sputum at Days 14, 28, 56 |
| End point description:<br>Neutrophil elastase activity in sputum was performed to treatment group for each scheduled visit. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline (Day 1), Day 14, 28 and 56   |  |

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[36]</sup> | 47 <sup>[37]</sup> |  |  |
| Units: units per liter               |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 44, 47)                 | 213.21 (± 229.235) | 250.21 (± 296.335) |  |  |
| Change at Day 14 (N= 38, 45)         | 34.62 (± 170.219)  | -22.29 (± 137.516) |  |  |
| Change at Day 28 (N= 40, 46)         | -6.76 (± 169.055)  | -24.84 (± 155.737) |  |  |
| Change at Day 56 (N= 34, 42)         | 11.89 (± 162.026)  | -41 (± 216.065)    |  |  |

Notes:

[36] - FAS population

[37] - FAS population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline of Human Neutrophil Elastase (NE) Concentration in Sputum at Days 14, 28, 56

|  |   |
|--|---|
| End point title  | Change From Baseline of Human Neutrophil Elastase (NE) Concentration in Sputum at Days 14, 28, 56 |
| End point description:<br>Neutrophil elastase concentration in sputum was performed to treatment group for each scheduled visit. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |   |
| End point type   | Secondary   |
| End point timeframe:<br>Baseline (Day 1), Day 14, 28 and 56  |   |

| End point values                     | BAY85-8501         | Placebo              |  |  |
|--------------------------------------|--------------------|----------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed          | 47 <sup>[38]</sup> | 47 <sup>[39]</sup>   |  |  |
| Units: microgram per liter           |                    |                      |  |  |
| arithmetic mean (standard deviation) |                    |                      |  |  |
| Baseline (N= 44, 47)                 | 24.567 (± 37.7496) | 39.215 (± 120.0264)  |  |  |
| Change at Day 14 (N= 38, 45)         | 21.261 (± 20.4157) | 32.79 (± 91.6294)    |  |  |
| Change at Day 28 (N= 40, 44)         | -7.59 (± 33.8392)  | -12.523 (± 112.9358) |  |  |
| Change at Day 56 (N= 34, 42)         | -2.282 (± 35.3634) | 16.033 (± 190.0303)  |  |  |

Notes:

[38] - FAS population

[39] - FAS population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: C-reactive Protein

|                 |  |
|-----------------|--|
| End point title | Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: C-reactive Protein |
|-----------------|--|

End point description:

Biomarkers in blood that were analyzed included C-reactive protein (hCRP). hCRP is an acute phase reactant protein. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. CRP is an acute phase reactant protein

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

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[40]</sup> | 47 <sup>[41]</sup> |  |  |
| Units: microgram per liter           |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 45, 45)                 | 7.47 (± 7.325)     | 11.66 (± 14.582)   |  |  |
| Change at Day 14 (N= 42, 44)         | -0.45 (± 4.584)    | 0.52 (± 8.834)     |  |  |
| Change at Day 28 (N= 44, 45)         | 2.9 (± 22.077)     | 2.46 (± 19.309)    |  |  |
| Change at Day 56 (N= 38, 42)         | -0.62 (± 8.329)    | 4.96 (± 19.868)    |  |  |

Notes:

[40] - FAS population

[41] - FAS population

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Biomarkers in Blood: Creactive Protein |
| Comparison groups                       | BAY85-8501 v Placebo                   |
| Number of subjects included in analysis | 94                                     |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | other                                  |
| P-value                                 | = 0.927                                |
| Method                                  | ANCOVA                                 |
| Parameter estimate                      | LS-mean Difference                     |
| Point estimate                          | 0.41                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | -8.539                                 |
| upper limit                             | 9.367                                  |

### Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Interleukin-8 (IL-8)

|   |  |
|---|--|
| End point title   | Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Interleukin-8 (IL-8) |
| End point description:  |  |
| Biomarkers in blood that were analyzed included IL-8. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline (Day 1), Day 14, 28 and 56   |  |

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[42]</sup> | 47 <sup>[43]</sup> |  |  |
| Units: nanogram per liter            |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 45, 45)                 | 46.97 (± 185.099)  | 18.86 (± 12.88)    |  |  |
| Change at Day 14 (N= 42, 45)         | 14.8 (± 109.806)   | 10.34 (± 51.355)   |  |  |
| Change at Day 28 (N= 44, 45)         | -29.85 (± 181.546) | 7.68 (± 32.687)    |  |  |
| Change at Day 56 (N= 38, 43)         | -35.19 (± 191.115) | 3.42 (± 39.332)    |  |  |

Notes:

[42] - FAS population

[43] - FAS population

## Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Biomarkers in Blood: Interleukin-8 |
| Comparison groups                       | BAY85-8501 v Placebo               |
| Number of subjects included in analysis | 94                                 |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | other                              |
| P-value                                 | = 0.0771                           |
| Method                                  | ANCOVA                             |
| Parameter estimate                      | LS-mean Difference                 |
| Point estimate                          | -9.56                              |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -20.188                            |
| upper limit                             | 1.063                              |

## Secondary: Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Neutrophil cell Count

|  |   |
|--|---|
| End point title  | Change From Baseline of Biomarkers in Blood at Days 14, 28, 56: Neutrophil cell Count |
| End point description:   |   |
| Biomarkers in blood that were analyzed included neutrophil cell count. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Baseline (Day 1), Day 14, 28 and 56  |   |

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[44]</sup> | 47 <sup>[45]</sup> |  |  |
| Units: giga per liter                |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 45, 47)                 | 4.331 (± 1.2776)   | 4.338 (± 1.4379)   |  |  |
| Change at Day 14 (N= 41, 45)         | -0.056 (± 0.9886)  | -0.257 (± 1.2292)  |  |  |
| Change at Day 28 (N= 44, 47)         | 0.122 (± 1.0209)   | -0.2 (± 1.4049)    |  |  |
| Change at Day 56 (N= 39, 43)         | -0.037 (± 0.9817)  | 0.377 (± 1.2587)   |  |  |

Notes:

[44] - FAS population

[45] - FAS population

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Biomarkers in Blood: Neutrophil cell Count |
| Comparison groups                       | BAY85-8501 v Placebo                       |
| Number of subjects included in analysis | 94   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | other                                      |
| P-value                                 | = 0.143                                    |
| Method                                  | ANCOVA                                     |
| Parameter estimate                      | LS-mean Difference                         |
| Point estimate                          | 1.86                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.643                                     |
| upper limit                             | 4.371                                      |

### Secondary: Change From Baseline of Biomarkers in Urine At Days 14, 28, 56: Creatinine

|   |  |
|---|--|
| End point title   | Change From Baseline of Biomarkers in Urine At Days 14, 28, 56: Creatinine |
| End point description:<br>Biomarker assessments included creatinine in the urine. Concentrations of creatinine was measured and reported. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline (Day 1), Day 14, 28 and 56   |  |

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[46]</sup> | 47 <sup>[47]</sup> |  |  |
| Units: micromole per liter           |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 42, 43)                 | 7328.1 (± 5135.68) | 7153.7 (± 4273.61) |  |  |
| Change at Day 14 (N= 39, 41)         | 1598.1 (± 6149.83) | 363.8 (± 2890.06)  |  |  |
| Change at Day 28 (N= 40, 39)         | 1221.8 (± 5070.3)  | 1856.5 (± 4082.98) |  |  |
| Change at Day 56 (N= 37, 40)         | 1064.9 (± 6227.38) | 948 (± 4387.41)    |  |  |



Notes:

[46] - FAS population

[47] - FAS population

### Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Biomarkers in Urine: Creatinine |
| Comparison groups                       | BAY85-8501 v Placebo            |
| Number of subjects included in analysis | 94                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | other                           |
| P-value                                 | = 0.5255                        |
| Method                                  | ANCOVA                          |
| Parameter estimate                      | LS-mean Difference              |
| Point estimate                          | -585.38                         |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -2413.24                        |
| upper limit                             | 1242.474                        |

### Secondary: Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Desmosine

|                 |   |
|-----------------|---|
| End point title | Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Desmosine |
|-----------------|---|

End point description:

Biomarker assessments included elastin degradation product desmosine in the urine. Desmosine was measured and reported. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

| End point values                     | BAY85-8501         | Placebo            |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[48]</sup> | 47 <sup>[49]</sup> |  |  |
| Units: nanogram per milliliter       |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 42, 43)                 | 10.816 (± 7.797)   | 12.812 (± 8.8276)  |  |  |
| Change at Day 14 (N= 39, 41)         | 2.262 (± 7.677)    | 0.371 (± 4.5118)   |  |  |
| Change at Day 28 (N= 40, 39)         | 2.744 (± 8.1192)   | 3.617 (± 5.9407)   |  |  |
| Change at Day 56 (N= 37, 40)         | 1.316 (± 9.6672)   | 1.577 (± 8.5245)   |  |  |

Notes:

[48] - FAS population

[49] - FAS population

### Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>       | Biomarkers in Urine: Desmosine |
| Comparison groups                       | BAY85-8501 v Placebo           |
| Number of subjects included in analysis | 94                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.3605                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | LS-mean Difference             |
| Point estimate                          | -1.44                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -4.545                         |
| upper limit                             | 1.673                          |

### Secondary: Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Normalized Desmosine Value to Creatinine

|                 |  |
|-----------------|--|
| End point title | Change From Baseline of Biomarkers in Urine at Days 14, 28, 56: Normalized Desmosine Value to Creatinine |
|-----------------|--|

End point description:

Normalized desmosine value to creatinine is the ratio obtained by calculating assay of desmosine divided by assay of creatinine. In the categories listed below, "N" signifies the number of subjects evaluable for the outcome.

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

End point timeframe:

Baseline (Day 1), Day 14, 28 and 56

|                                      |                    |                    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| <b>End point values</b>              | BAY85-8501         | Placebo            |  |  |
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 47 <sup>[50]</sup> | 47 <sup>[51]</sup> |  |  |
| Units: nanogram per milligram        |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Baseline (N= 42, 43)                 | 13.926 (± 5.4532)  | 15.674 (± 4.2885)  |  |  |
| Change at Day 14 (N= 39, 41)         | 0.227 (± 4.227)    | 0.081 (± 3.4887)   |  |  |
| Change at Day 28 (N= 40, 39)         | 0.609 (± 3.6745)   | 0.651 (± 2.9772)   |  |  |
| Change at Day 56 (N= 37, 40)         | 0.096 (± 4.1133)   | 0.03 (± 4.4286)    |  |  |

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Notes:

[50] - FAS population

[51] - FAS population

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Normalized Desmosine Value to Creatinine |
| Comparison groups                       | BAY85-8501 v Placebo                     |
| Number of subjects included in analysis | 94                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other                                    |
| P-value                                 | = 0.7666                                 |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | LS-mean Difference                       |
| Point estimate                          | -0.23                                    |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1.756                                   |
| upper limit                             | 1.299                                    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to follow-up visit (28 days after last dose)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | BAY85-8501 |
|-----------------------|------------|

Reporting group description:

Daily oral dose of 1 mg BAY85-8501 tablets for 28 days.

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

Reporting group description:

Placebo-matched to BAY85-8501 for 28 days.

| Serious adverse events                            | BAY85-8501     | Placebo        |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 3 / 45 (6.67%) | 1 / 47 (2.13%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Cardiac disorders                                 |                |                |  |
| Accelerated idioventricular rhythm                |                |                |  |
| subjects affected / exposed                       | 0 / 45 (0.00%) | 1 / 47 (2.13%) |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders   |                |                |  |
| Apnoeic attack                                    |                |                |  |
| subjects affected / exposed                       | 1 / 45 (2.22%) | 0 / 47 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Bronchiectasis                                    |                |                |  |
| subjects affected / exposed                       | 1 / 45 (2.22%) | 0 / 47 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |
| Infections and infestations                       |                |                |  |
| Bronchopneumonia                                  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 47 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | BAY85-8501       | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 18 / 45 (40.00%) | 20 / 47 (42.55%) |  |
| Nervous system disorders                              |                  |                  |  |
| Headache  |                  |                  |  |
| subjects affected / exposed                           | 5 / 45 (11.11%)  | 4 / 47 (8.51%)   |  |
| occurrences (all)                                     | 9                | 6                |  |
| Gastrointestinal disorders                            |                  |                  |  |
| Nausea  |                  |                  |  |
| subjects affected / exposed                           | 1 / 45 (2.22%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                                     | 1                | 3                |  |
| Diarrhoea   |                  |                  |  |
| subjects affected / exposed                           | 4 / 45 (8.89%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                                     | 6                | 4                |  |
| Vomiting  |                  |                  |  |
| subjects affected / exposed                           | 3 / 45 (6.67%)   | 0 / 47 (0.00%)   |  |
| occurrences (all)                                     | 4                | 0                |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                  |  |
| Cough   |                  |                  |  |
| subjects affected / exposed                           | 4 / 45 (8.89%)   | 4 / 47 (8.51%)   |  |
| occurrences (all)                                     | 5                | 4                |  |
| Sputum increased                                      |                  |                  |  |
| subjects affected / exposed                           | 3 / 45 (6.67%)   | 3 / 47 (6.38%)   |  |
| occurrences (all)                                     | 3                | 3                |  |
| Musculoskeletal and connective tissue disorders       |                  |                  |  |
| Muscle spasms   |                  |                  |  |
| subjects affected / exposed                           | 3 / 45 (6.67%)   | 0 / 47 (0.00%)   |  |
| occurrences (all)                                     | 5                | 0                |  |
| Infections and infestations                           |                  |                  |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Nasopharyngitis                         |                |                 |  |
| subjects affected / exposed             | 2 / 45 (4.44%) | 6 / 47 (12.77%) |  |
| occurrences (all)                       | 2              | 6               |  |
| Viral upper respiratory tract infection |                |                 |  |
| subjects affected / exposed             | 3 / 45 (6.67%) | 1 / 47 (2.13%)  |  |
| occurrences (all)                       | 3              | 1               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 08 November 2012 | Measurement of the concentration of neutrophil elastase in the sputum was added as a biomarker endpoint. This endpoint allowed direct measurement of NE concentration (in sputum) as a biomarker endpoint; it was inadvertently omitted in the final stage of protocol preparation. |

Notes:

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### 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.

|  |
|--|
| Decimal places were automatically truncated if last decimal equals zero. |
|--|

Notes: