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Name of company: Boehringer Ingelheim		Synopsis	Boehringer Ingelheim
BI proprietary name: Not applicable			
BI investigational product: Not applicable		**Page:** 1 of 9	
Report date: Disclosure Synopsis	**Trial no./Doc. no.:** 0352-2069	**Dates of trial:** 22 Jul 2016 – 16 Jun 2021	**Date of revision:** Not applicable

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Title of trial

Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years [FOOTPRINTS®]

Lay title

FOOTPRINTS®: A study in healthy people and people with chronic obstructive pulmonary disease (COPD) to look at factors that lead to emphysema progression

Project Advisor

[redacted] USA

Trial sites with screened subjects

Multinational study in 51 sites (with 688 screened subjects) in 12 countries in North America, Europe, and Japan/South Korea

Publications

Crapo JD, Gupta A, Lynch DA, et al. BMJ Open 2021;11:e042526

Crapo JD, Gupta A, Lynch DA, et al. Am J Respir Crit Care Med 2020;201:A2868

Crapo JD, Gupta A, Lynch DA, et al., Poster A2868, International Conference of the American Thoracic Society, from 15 May to 20 May 2020, Philadelphia

Clinical phase: Not applicable

Objectives

The overall objective of this study was to explore, if any of the biomarkers (soluble, imaging, and physiological) assessed within ex-smoking controls, patients with chronic obstructive pulmonary disease (COPD) and patients with COPD and A1AT deficiency (A1ATD) were correlated to COPD disease progression, particularly emphysema progression over 156 weeks.

Methodology

Prospective, longitudinal study

Number of subjects

Planned:	Entered: up to 455 subjects
Actual:	Screened: 688
	Entered: 463

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Number of subjects (cont.)

Subjects entered and analysed for the primary endpoint[1]:

Study group	Entered	Analysed
Ex-smoking controls	62	61
Patients with COPD GOLD[2] 1	123	122
Patients with COPD GOLD 2	130	127
Patients with COPD GOLD 3	130	127
Patients with COPD and A1ATD	19	19

1 In this study primary endpoints were referred to as main outcome measures.

2 GOLD = Global Initiative for Chronic Obstructive Lung Disease

Study population

Ex-smokers without airway obstruction; COPD GOLD grade 1, 2, 3; COPD and A1ATD (ZZ genotype)

Main criteria for inclusion

- Ex-smoking controls of both sexes aged ≥40 and ≤70 years, with a smoking history ≥20 pack years, and a body mass index (BMI) of ≥18 and ≤35 kg/m^2 (≤30 kg/m^2 in the MRI substudy)
- Patients with mild, moderate, and severe COPD of both sexes aged ≥40 and ≤70 years, with a smoking history ≥20 pack years, and BMI of ≥18 and ≤35 kg/m^2 (≤30 kg/m^2 in the MRI substudy)
- Patients with mild, moderate, and severe COPD and A1ATD of both sexes aged ≥30 and ≤70 years, with a smoking history ≥10 pack years, and BMI of ≥18 and ≤35 kg/m^2

BI investigational product: No investigational medicinal product was administered in this study.

Duration of observation

156 weeks (about 3 years)

Clinical criteria and biomarker for evaluation

Main outcome measures

- Absolute change from baseline in lung density based on PD15 adjusted for lung volume (ALD) [g/L/year] (up to Week 156)
- Annual rate of lung function decline based on FEV_1 [mL/year] (up to Week 156)
- Number of exacerbations per year [days] (up to Week 156)
- Duration of exacerbations per year [days] (up to Week 156)
- Occurrence of an at least moderate exacerbation during study (up to Week 156)
- Occurrence of a severe exacerbation during study (up to Week 156)

Further assessments

Lung function assessments

- Spirometry: FEV_1, FEV_1 percent predicted (pp), FVC, FVC pp, FEV_1/FVC, FEV_1/FVC pp, FEF_{25-75}
- Body plethysmography: TLC, IC, IC/TLC, RV, RV pp, ERV, IVC, FRC

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Clinical criteria and biomarker for evaluation (cont.)

- Diffusing capacity of the lung for carbon monoxide: DLCO, DLCO corrected for haemoglobin (Hb), DLCO predicted, DLCO pp, VA, DLCO/VA, DLCO/VA corrected for Hb

Imaging assessments

- Chest computed tomography (CT):
  - Qualitative CT for total lung:
    Non-emphysematous air trapping, increased airway thickness, centrilobular emphysema, paraseptal emphysema, bullae, bronchiectasis, bronchiectasis predominant pattern, mucoid impaction, predominant distribution of mucoid impaction, tracheomalacia, pneumothorax, mosaic attenuation
  - Quantitative CT for total lung, the left lung, the right lung, the left upper lobe, the left lower lobe, the right upper lobe, the right middle lobe, and the right lower lobe:
    Histogram percentile inspiratory, histogram percentile expiratory, inspiratory volume, expiratory volume, emphysema score (total lung, upper lobes, lower lobes, ratio of upper/lower lobes), air trapping score (total lung, upper lobes, lower lobes, ratio of upper/lower lobes), mean lung density on inspiratory scan, mean lung density on expiratory scan, airway lumen perimeter, airway lumen diameter, airway wall area for sub-segmental and segmental airways, wall thickness for sub-segmental and segmental airways, lung micro mapping (LMM) emphysema, LMM air trapping, LMM normal, FRC/TLC ratio (calculated as expiratory volume/inspiratory volume)

Biofluid assessments

- Soluble biomarkers from blood (whole blood, plasma, serum):
- Induced sputum (at selected sites):
  - Percentage of cells per total non-squamous cells: macrophages, neutrophils, eosinophils, lymphocytes, bronchial epithelial cells, monocytes
- Symptom questionnaires (patients with COPD and patients with COPD and A1ATD): modified British Medical Research Council questionnaire (mMRC), COPD Assessment Test questionnaire (CAT), St George's Respiratory Questionnaire (SGRQ)

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Clinical criteria and biomarker for evaluation (cont.)

- Medical Events of Special Interest (MESIs): respiratory (including COPD exacerbations), cardiovascular, metabolic/digestive, neurological/psychiatric, and other disorders (at the discretion of the investigator)

Other assessments

- Pulse oximetry: SpO_2 [%]
- BODE index (patients with COPD and patients with COPD and A1ATD): total score
- 6-minute walk test: total distance, reason for stopping prematurely, requirement of walking aid

Safety criteria for evaluation

- Procedure-related adverse events
- Vital signs, physical examination, safety laboratory, urine pregnancy testing, and 12-lead electrocardiogram (ECG)

Statistical methods

ALD change from baseline was evaluated using a mixed model for repeated measurements (MMRM). The annual rate of decline in FEV_1 was analysed by performing a restricted maximum likelihood based approach using a random slope and intercept model. The main outcome measures concerning exacerbations (number, duration, occurrence of an at least moderate and of a severe exacerbation up to Week 156) were analysed by descriptive and summary statistics. Further outcome measures were analysed by descriptive and summary statistics (for the soluble biomarkers and the imaging parameters a log2-transformation was applied), Spearman correlation analyses, MMRM models to establish time profiles, linear and logistic regression analyses, [redacted].

Two interim analyses were planned and conducted after data from the 52-week and 104-week assessment were available for at least 70% of subjects entered in the study. Based on the first and on the second interim analysis an ‘other clinical report’ was written respectively.

SUMMARY - CONCLUSIONS

Trial subjects and compliance with the clinical study protocol

A total of 688 subjects were screened. Of these, 463 subjects were entered and included in the observed subjects set (OBS: 62 ex-smoking controls, 123 patients with GOLD stage 1, 130 patients with GOLD stage 2, 129 patients with GOLD stage 3, 19 patients with COPD and A1ATD), whereas 225 subjects were not found eligible for the study, mainly because they did not meet all inclusion criteria and/or fulfilled any exclusion criterion, or the recruitment was closed for the respective diagnosis group. Overall, 370 subjects (79.9%) completed the study. Six ex-smoking controls (9.7%), 78 patients (20.4%) of the GOLD 1-3 group, and 9 patients (47.4%) with COPD and A1ATD prematurely discontinued participation in the study mainly due to ‘other reasons’ (12.3%) and ‘consent withdrawn’ (4.3%, Table 1). Of the 463 subjects in the OBS, 7 subjects were not included in the per-protocol set biomarker subjects (PPSBM) due to important protocol deviations.

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Trial subjects and compliance with the clinical study protocol (cont.)

Table 1 Subject disposition by diagnosis group - OBS

	Ex-smoking controls N (%)	GOLD 1 N (%)	GOLD 2 N (%)	GOLD 3 N (%)	GOLD 1-3[1] N (%)	A1ATD N (%)	Total N (%)
Entered	62 (100.0)	123 (100.0)	130 (100.0)	129 (100.0)	382 (100.0)	19 (100.0)	463 (100.0)
Completed	56 (90.3)	101 (82.1)	110 (84.6)	93 (72.1)	304 (79.6)	10 (52.6)	370 (79.9)
2-years	2 (3.2)	1 (0.8)	1 (0.8)	3 (2.3)	5 (1.3)	0	7 (1.5)
Discontinued	6 (9.7)	22 (17.9)	20 (15.4)	36 (27.9)	78 (20.4)	9 (47.4)	93 (20.1)
Adverse event[2]	0	0	0	3 (2.3)	3 (0.8)	0	3 (0.6)
Non compliant with protocol	0	3 (2.4)	0	2 (1.6)	5 (1.3)	0	5 (1.1)
Lost to follow-up	0	4 (3.3)	1 (0.8)	3 (2.3)	8 (2.1)	0	8 (1.7)
Consent withdrawn	5 (8.1)	3 (2.4)	6 (4.6)	6 (4.7)	15 (3.9)	0	20 (4.3)
Other[3]	1 (1.6)	12 (9.8)	13 (10.0)	22 (17.1)	47 (12.3)	9 (47.4)	57 (12.3)
COVID-19 related	0	3 (2.4)	4 (3.1)	1 (0.8)	8 (2.1)	6 (31.6)	14 (3.0)

1 A1ATD patients are not included in the GOLD 1-3 column.

2 In this observational study only procedure-related AEs were collected.

3 Category includes also discontinuation because of MESI

In total, 294 subjects (64.5%) in the PPSBM were male. The majority of subjects was White (90.1%). Asian race was reported for 7.9% of all subjects. Only 1.5% of all subjects were Hispanic or Latino. The mean age was similar for the subjects of the 3 different GOLD groups, but higher compared with the mean age of ex-smoking controls and the A1ATD group (see Table 2). Overall, a mean of 43.1 pack years (SD 19.5) was reported. The mean pack years ranged from 25.2 pack years (SD 12.3) in the A1ATD group to 49.2 pack years (SD 21.6) in the GOLD 3 group. In total, 221 of all entered subjects (47.7%) had ≥1 important protocol deviation (iPD). The number of subjects with iPDs was highest in the GOLD 3 group (63.6%) and lowest in ex-smoking controls (32.3%), in both cases mainly driven by ‘concomitant medication’ (GOLD 3: 55.8%; ex-smoking controls: 21.0%).

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Trial subjects and compliance with the clinical study protocol (cont.)

Table 2 Demographic data by diagnosis group - PPSBM

	Ex-smoking controls N (%)	GOLD 1 N (%)	GOLD 2 N (%)	GOLD 3 N (%)	GOLD 1-3[1] N (%)	A1ATD N (%)	Total N (%)
Number of subjects, N (%)	61 (100.0)	122 (100.0)	127 (100.0)	127 (100.0)	376 (100.0)	19 (100.0)	456 (100.0)
Sex, N (%)							
Male	38 (62.3)	85 (69.7)	76 (59.8)	79 (62.2)	240 (63.8)	16 (84.2)	294 (64.5)
Female	23 (37.7)	37 (30.3)	51 (40.2)	48 (37.8)	136 (36.2)	3 (15.8)	162 (35.5)
Race, N (%)							
American Indian or Alaska Native	0	0	1 (0.8)	1 (0.8)	2 (0.5)	0	2 (0.4)
Asian	8 (13.1)	16 (13.1)	6 (4.7)	6 (4.7)	28 (7.4)	0	36 (7.9)
Black or African American	1 (1.6)	1 (0.8)	3 (2.4)	2 (1.6)	6 (1.6)	0	7 (1.5)
White	52 (85.2)	105 (86.1)	117 (92.1)	118 (92.9)	340 (90.4)	19 (100.0)	411 (90.1)
Ethnicity							
Hispanic or Latino	0	2 (1.6)	1 (0.8)	3 (2.4)	6 (1.6)	1 (5.3)	7 (1.5)
Not Hispanic or Latino	60 (98.4)	120 (98.4)	124 (97.6)	122 (96.1)	366 (97.3)	18 (94.7)	444 (97.4)
Missing	1 (1.6)	0	2 (1.6)	2 (1.6)	4 (1.1)	0	5 (1.1)
Age, mean (SD) [years]	53.9 (6.8)	62.0 (6.2)	61.8 (5.4)	62.9 (5.6)	62.2 (5.8)	52.8 (9.0)	60.7 (6.9)

Baseline ALD

At baseline, the median of ALD was 89.45 g/L in ex-smoking controls (minimum [min]: 62.3 g/L, maximum [max]: 113.7 g/L). In patients with COPD, median baseline ALD decreased with increasing of COPD severity (GOLD 1: 87.47 g/L, min: 28.4 g/L, max: 137.9 g/L; GOLD 2: 73.48 g/L, min: 12.1 g/L, max: 137.2 g/L; GOLD 3: 53.89 g/L, min: 6.8 g/L, max: 109.3 g/L) and was lowest in the A1ATD group (50.07 g/L, min: 24.1 g/L, max: 90.4 g/L).

Clinical and biomarker assessment results

ALD change from baseline up to Week 156

At Week 52, a significant decrease of ALD compared with baseline was seen in the GOLD 3 group (adjusted mean changes from baseline: -1.85 g/L; 95% CI -3.48, -0.22; p = 0.0267) and in the A1ATD group (adjusted mean changes from baseline: -4.13 g/L; 95% CI -7.90, -0.35, p = 0.0323). At Week 104 and Week 156, there was a significant decrease of ALD from baseline in all GOLD groups (adjusted mean changes from baseline at Week 104: GOLD 1: -2.74 g/L, 95% CI -4.13, -1.35, p< = 0.0001; GOLD 2: -3.63 g/L, 95% CI -5.09, -2.17; p<0.0001; GOLD 3: -2.96 g/L, 95% CI -4.76, -1.16; p = 0.0014; at Week 156: GOLD 1: -3.15 g/L, 95% CI -4.71, -1.60, p<0.0001; GOLD 2: -5.04 g/L, 95% CI -6.70, -3.39; p<0.0001; GOLD 3: -4.74 g/L, 95% CI -6.79, -2.69; p<0.0001) and in the A1ATD group (adjusted mean at Week 104: -6.39 g/L; 95% CI -10.06, -2.72; p = 0.0007; at Week 156: -6.13 g/L; 95% CI -11.08, -1.18;

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Clinical and biomarker assessment results (cont.)

p = 0.0155). No significant ALD change from baseline was seen in ex-smoking controls at any of the timepoints (adjusted mean change from baseline at Week 156: -0.27 g/L: 95% CI -2.23, 1.70).

At Week 52, the ALD change from baseline differed significantly between patients of the GOLD 3 group and ex-smoking controls (adjusted mean vs. ex-smoking controls: -2.70 g/L, 95% CI -5.25, -0.16; p = 0.0375). At Week 104 a significant difference was found for patients of the GOLD 2 group compared with ex-smoking controls (adjusted mean vs. ex-smoking controls: -2.57 g/L; 95% CI -4.93, -0.20; p = 0.0333). At Week 156, there was a significant difference of ALD change from baseline between all GOLD groups and ex-smoking controls (adjusted mean vs. ex-smoking controls: GOLD 1: -2.89 g/L, 95% CI -5.32, 0.45, p = 0.0202; GOLD 2: -4.78 g/L, 95% CI -7.36, -2.19, p = 0.0003; GOLD 3: -4.47 g/L, 95% CI -7.44, -1.50; p = 0.0033). Comparison of patients of the A1ATD group with ex-smoking controls showed a significant different ALD change from baseline at Weeks 52, 104, and 156 with adjusted mean differences of -4.99 g/L (95% CI -9.25, -0.72; p = 0.0221), -5.33 g/L (95% CI -9.56, -1.10, p = 0.0138), and -5.86 g/L (95% CI -11.26, -0.47; p = 0.0334), respectively.

Annual rate of decline in FEV_1

A significant annual rate of decline in FEV_1 was seen in ex-smoking controls (unadjusted rate: -25.7 mL/yr, 95% CI -48.1, -3.3) and in all patient groups (unadjusted rates GOLD 1: -24.4 ml/yr, -42.0, -6.8; GOLD 2: -44.9 mL/yr, 95% CI -63.8, -25.9; GOLD 3: -59.3 mL/yr, 95% CI -81.8, -36.8; A1ATD: -87.5 mL/yr, 95% CI -142.6, -32.3), whereby the decline was greater with increasing severity of the GOLD stage and was largest in the A1ATD group.

Compared with ex-smoking controls, a significant larger annual rate of decline in FEV_1 was seen in patients of the GOLD 3 group (unadjusted difference: -33.6 mL/yr, 95% CI -65.4, -1.9, p = 0.0381) and in patients of the A1ATD group (unadjusted difference: -61.8 mL/yr, 95% CI -121.3, -2.3, p = 0.0419). Comparison of ex-smoking controls vs. patients of the GOLD 1, and GOLD 2 groups did not reveal any significant differences in annual rates of decline in FEV_1, unadjusted differences were 1.3 mL/yr (95% CI -27.2, 29.7; p = 0.9306) and -19.2 mL/yr (95% CI -48.5, 10.1; p = 0.1983), respectively.

Exacerbations of COPD up to Week 156

Ex-smoking controls had almost no COPD exacerbation per year (mean number: 0.02/year, SD: 0.13). In patients of the GOLD 1-3 group a mean of 0.36 exacerbations (SD: 0.53) per year was reported whereby the number of exacerbations was higher with increasing severity of GOLD stages. Patients of the A1ATD group had a mean of 0.79 exacerbations per year (SD: 0.60). The mean duration of exacerbation ranged from 9.7 days (SD: 13.0) in patients of the GOLD 1 group to 19.7 days (SD: 24.2) in the GOLD 3 group and it was 17.8 days (SD: 16.7) in patients of the A1ATD group and 13.1 days (SD: 5.2) in ex-smoking controls. Only 1 ex-smoking control person experienced 1 moderate exacerbation. The majority of patients in the GOLD 1 and GOLD 2 groups had mild exacerbations whereas the majority of patients in the GOLD 3 group (79 patients, 62.2%) and in the A1ATD group (15 patients, 78.9%) had at least moderate exacerbations. In addition, the number of patients with at least 2 moderate exacerbations was greater with increasing GOLD stages. The number of patients with severe exacerbations ranged from 2 patients (1.6%) in the GOLD 1 group to 24 patients (18.9%) in the GOLD 3 group. Three patients in the A1ATD group (15.8%) had severe exacerbations.

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Clinical and biomarker assessment results (cont.)

Table 3 Descriptive summary for number of exacerbations per year, duration, and severity by diagnosis group - PPSBM

	ex-smoking controls	GOLD 1	GOLD 2	GOLD 3	GOLD 1-3	A1ATD
Number of subjects, N (%)	61 (100.0)	122 (100.0)	127 (100.0)	127 (100.0)	376 (100.0)	19 (100.0)
Number of exacerbations per year, mean (SD)	0.02 (0.13)	0.15 (0.36)	0.34 (0.45)	0.58 (0.65)	0.36 (0.53)	0.79 (0.60)
Duration of exacerbations per year [days]						
Number of analysed subjects, N (%)	2	33	61	86	180	17
Mean (SD)	13.1 (5.2)	9.7 (13.0)	18.0 (19.4)	19.7 (24.2)	17.3 (21.1)	17.8 (16.7)
Number of at least moderate exacerbations during study, N (%)						
0	60 (98.4)	93 (76.2)	73 (57.5)	48 (37.8)	214 (56.9)	4 (21.1)
1	1 (1.6)	20 (16.4)	22 (17.3)	29 (22.8)	71 (18.9)	8 (42.1)
≥2	0	9 (7.4)	32 (25.2)	50 (39.4)	91 (24.2)	7 (36.8)
Number of severe exacerbations during study, N (%)						
0	61 (100.0)	120 (98.4)	118 (92.9)	103 (81.1)	341 (90.7)	16 (84.2)
1	0	1 (0.8)	9 (7.1)	19 (15.0)	29 (7.7)	1 (5.3)
≥2	0	1 (0.8)	0	5 (3.9)	6 (1.6)	2 (10.5)

Lung function parameters over time

Changes of lung function parameters over time were evaluated using an REML based MMRM. In patients of the GOLD 1-3 group, there was a significant decrease from baseline to Week 156 for FEV_1, percent predicted FEV_1, FVC, percent predicted FVC, FEV_1/FVC, percent predicted FEV_1/FVC, FEF_{25-75}, IVC, IC, RV, percent predicted RV, ERV, VA, and DLCO/VA.

Medical events of special interest

Overall, 321 subjects (70.4%) experienced at least 1 MESI during the observational period. At least 1 MESI was reported for 37.7% of ex-smoking controls and for 74.5% of patients in the GOLD 1-3 group, whereby the percentage of patients with MESIs was higher with increasing severity of COPD. Almost all patients with COPD and A1ATD (94.7%) were reported with at least 1 MESI. During the observational period, the most frequently reported MESI categories were COPD exacerbation (43.6%), osteoporosis (14.0%), and 'other' (36.4%). On the preferred term level, MESIs reported with an incidence of >10% in any diagnosis group were COPD, osteoporosis, pulmonary mass, upper respiratory tract infection, and pneumonia. Most

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MESIs were classified as mild or moderate (224 out of 456 subjects, 49.1%), while 97 out of 456 patients (21.3%) were reported with severe MESIs. Fifteen patients had MESIs leading to death including 3 patients in the GOLD 1 group (1 patient each with circulatory collapse and respiratory failure, cerebrovascular disorder, no reason given), 4 patients in the GOLD 2 group (1 patient each with COVID-19, thrombosis; no reason given for 2 patients), and 8 patients in the GOLD 3 group (3 patients with malignant lung neoplasm; 1 patient each with chronic respiratory failure, multiforme glioblastoma, pneumonia; 1 patient with the 6 MESIs aneurysm, acute respiratory failure, brain oedema, shock, subarachnoid haemorrhage, and pneumonia; 1 patient with the 2 MESIs circulatory collapse and respiratory failure).

Safety results

Procedure-related AEs were analysed on the OBS.

At least 1 procedure-related AE was reported for 41 of 463 subjects (8.9%). Of these, 7 subjects (11.3%) were ex-smoking controls, and 34 subjects (8.9%) belonged to the GOLD 1-3 group. The frequency of procedure-related AEs increased with increasing severity of the GOLD stage: 5 patients (4.1%) in the GOLD 1 group, 10 patients (7.7%) in the GOLD 2 group, and 19 patients (14.7%) in the GOLD 3 group. No AEs were reported in patients with COPD and A1ATD. None of the procedure-related AEs was severe, leading to study discontinuation, serious, leading to death, or considered other significant.

On system organ class level, injury, poisoning and procedural complications (2.6%), investigations (2.4%), and respiratory, thoracic and mediastinal disorders (2.2%) were reported most frequently overall. On preferred term level, ‘forced expiratory volume decreased’ was the only procedure-related AE occurring with a total incidence >2%.

Conclusions

In patients with COPD (GOLD stages 1-3), ALD decreased from baseline up to Weeks 52, 104, and 156. The change of ALD from baseline was significantly different between patients of the GOLD 1-3 group and ex-smoking controls at all these time points.

FEV_1 declined over 156 weeks both in ex-smoking controls and in patients. A significantly larger annual rate of decline in FEV_1 was seen in patients of the GOLD 3 group and in patients of the A1ATD group compared with ex-smoking controls.

The number of COPD exacerbations, their duration, and their severity were higher in patients with increasing severity of COPD.

Compared with ex-smoking controls, MESIs were reported about twice as often in patients with COPD with the frequency of MESIs increasing with increasing severity of COPD. Procedure-related AEs did not reveal any safety concern.