Supplementary text 1. Participant enrolment and retention, sample size calculation, and power calculations for annual decline in forced expiratory volume in 1 second and 15th percentile density assessed by CT

To achieve adequate participant enrolment, a recruitment plan was set up prior to the start of recruitment; this detailed the number of subjects expected at each site across the different study populations, and was based on feedback during site feasibility assessments. This plan was monitored constantly during the recruitment phase to track planned versus actual enrolment numbers. Local approaches to facilitate recruitment, such as advertising, were also used. To promote participant retention, a comprehensive strategy was set up during the course of the study. This included maintaining frequent contact with study participants (especially from Visits 5 to 7, where visits are 1 year apart), for example via phonecalls and greetings cards, as well as awareness training for site staff.

As this study is exploratory in nature, sample size calculations are focused on achieving the desired precision for biomarker estimates and relevant clinical assessments in all COPD patient groups except for the A1ATD group. This study planned to enrol 125 patients with mild COPD, 125 with moderate COPD and 125 with severe COPD – by assuming a ≤20% dropout rate after 3 years, at least 100 subjects per group are expected to contribute to the analysis by the end of the study period.

For annual decline in forced expiratory volume in 1 second (FEV_1), available information reports standard deviations (SDs) ranging from about 20 mL/year [1] to 60 mL/year.[2] Using this information and considering a planned 100 subjects in each group, supplementary table 1 reports the coverage probability for the half-width of a 95% confidence interval (CI) for annual FEV_1 decline for a given SD. For

example, if the observed SD is 50 mL/year, and the true half-width of the CI is 11 mL/year, with 100 subjects, the probability that the observed CI covers the true CI is 93.8%. The reported SD on annual decline in 15th percentile density (PD15) ranges from 3.4 g/L [3] to 5.5 g/L.[4] Using the same assumptions as for FEV_1 decline, we report the coverage probability of a true CI for a given SD and half-width of the CI for 100 subjects (supplementary table 2).

In addition, with 100 subjects in each group, and allowing for up to 15 covariates, a partial Pearson correlation coefficient of 0.30 can be declared significant with 80% power between any two continuous variables (e.g. FEV_1 and a new biomarker) within the group.

Supplementary table 1. Study sites

Study site and address
United States, Alabama
University of Alabama at Birmingham Birmingham, Alabama, United States, 35294
United States, California
University of California San Diego San Diego, California, United States, 92103-8415
The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center Torrance, California, United States, 90502
United States, Colorado
National Jewish Health Denver, Colorado, United States, 80206
United States, Iowa
University of Iowa Hospitals and Clinics Iowa City, Iowa, United States, 52242
United States, Maryland
Johns Hopkins University Baltimore, Maryland, United States, 21224
United States, Massachusetts
Brigham and Women's Hospital Boston, Massachusetts, United States, 02115

Study site and address
United States, Pennsylvania
Temple University Hospital Philadelphia, Pennsylvania, United States, 19140
United States, Texas
Baylor College of Medicine Houston, Texas, United States, 77030
Diagnostics Research Group San Antonio, Texas, United States, 78229
United States, Utah
University of Utah Health Sciences Center Salt Lake City, Utah, United States, 84108
Belgium
Brussels – UNIV St-Pierre Brussels, Belgium, 1000
UZ Leuven Leuven, Belgium, 3000
Canada, Alberta
University of Alberta Hospital (University of Alberta) Edmonton, Alberta, Canada, T6G 1Z1
Canada, Ontario
Saint Joseph's Healthcare Hamilton, Ontario, Canada, L8N 4A6
McMaster University Medical Centre Hamilton, Ontario, Canada, L8N 4K1

Study site and address
Canada, Quebec
McGill University Health Centre (MUHC) Montreal, Quebec, Canada, H4A 3J1
Canada, Saskatchewan
Royal University Hospital Saskatoon, Saskatchewan, Canada, S7N 0W8
Canada
IUCPQ (Laval University) Quebec, Canada, G1V 4G5
Denmark
Aarhus University Hospital, Skejby Aarhus N, Denmark, 8200
Gentofte Hospital Hellerup, Denmark, 2900
Hvidovre Hospital Hvidovre, Denmark, 2650
Finland
HYKS Keuhkosairauksien tutkimusyksikkö Helsinki, Finland, 00029
TYKS, Keuhkosairauksien klinikka, Turku Turku, Finland, 20520
Germany
IKF Pneumologie GmbH & Co. KG Frankfurt, Germany, 60596

Study site and address
Pneumologisches Forschungsinstitut an der LungenClinic Grosshansdorf GmbH Grosshansdorf, Germany, 22927
Fraunhofer ITEM Hannover, Germany, 30625
KLB Gesundheitsforschung Lübeck GmbH Lübeck, Germany, 23552
Japan
Kagoshima University Medical And Dental Hospital Kagoshima, Kagoshima, Japan, 890-8520
Showa University Fujigaoka Hospital Kanagawa, Yokohama, Japan, 227-8501
Kishiwada City Hospital Osaka, Kishiwada, Japan, 596-8501
Osaka City University Hospital Osaka, Osaka, Japan, 545-8586
Showa University Hospital Tokyo, Shinagawa-ku, Japan, 142-8666
Republic of Korea
Konkuk University Medical Center Seoul, Republic of Korea, 05030
SMG-SNU Boramae Medical Center Seoul, Republic of Korea, 07061
Korea University Guro Hospital Seoul, Republic of Korea, 08308

Study site and address
The Catholic University of Korea, Eunpyeong St. Mary's Hospital Seoul, Republic of Korea, 22711
Poland
Respiratory Medicine Centre, private prac., Bialystok Bialystok, Poland, 15044
University Clinical Center, Gdansk Gdansk, Poland, 80 952
Institute of Tuberculosis & Lung Disease, Warsaw Warsaw, Poland, 01138
Spain
Hospital del Mar Barcelona, Spain, 08003
Hospital Vall d'Hebron Barcelona, Spain, 08035
Hospital Clínic de Barcelona Barcelona, Spain, 08036
Hospital de Bellvitge L'Hospitalet de Llobregat, Spain, 08907
Hospital Son Espases Palma de Mallorca, Spain, 07010
Hospital Quirónsalud Madrid Pozuelo de Alarcón, Spain, 28223
Sweden
Skånes universitetssjukhus, Lund Lund, Sweden, 221 85

Study site and address
United Kingdom
Queen Elizabeth Hospital Birmingham, United Kingdom, B15 2GW
Glenfield Hospital Leicester, United Kingdom, LE3 9QP
Royal Free Hospital London, United Kingdom, NW3 2PF
Medicines Evaluation Unit Manchester, United Kingdom, M23 9QZ

Supplementary table 2. Coverage probability of 95% CIs for FEV_1 annual decline based on 100 subjects

	Half-width of a 95% CI									
SD	6	7	8	9	10	11	12	13	14	15
25	0.998	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
30	0.557	0.993	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
35	0.026	0.557	0.983	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
40	<0.001	0.048	0.557	0.97	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
45	<0.001	<0.001	0.072	0.557	0.954	>0.999	>0.999	>0.999	>0.999	>0.999
50	<0.001	<0.001	0.003	0.097	0.557	0.938	0.998	>0.999	>0.999	>0.999
55	<0.001	<0.001	<0.001	0.006	0.122	0.557	0.921	0.996	>0.999	>0.999
60	<0.001	<0.001	<0.001	<0.001	0.011	0.146	0.557	0.905	0.993	>0.999
65	<0.001	<0.001	<0.001	<0.001	<0.001	0.018	0.168	0.557	0.889	0.988
70	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.026	0.189	0.557	0.873

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

Supplementary table 3. Coverage probability of 95% CIs for PD15 annual decline based on 100 subjects

	Half-width of a 95% CI										
SD	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	0.95	1.00	1.05
2.5	0.938	0.998	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
3.0	0.146	0.557	0.905	0.993	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999	>0.999
3.5	0.001	0.026	0.189	0.557	0.873	0.983	0.999	>0.999	>0.999	>0.999	>0.999
4.0	<0.001	<0.001	0.005	0.048	0.226	0.557	0.846	0.970	0.997	>0.999	>0.999
4.5	<0.001	<0.001	<0.001	<0.001	0.011	0.072	0.257	0.557	0.822	0.954	0.993
5.0	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.021	0.097	0.284	0.557	0.801
5.5	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.006	0.033	0.122	0.306
6.0	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.011	0.048

CI, confidence interval; PD15, lung density at the 15th percentile point of the CT histogram; SD, standard deviation.

Supplementary table 4. Overview of permitted and restricted medications/therapy

Drug class	Prior to Visit 1	Between Visits 1 and 2	Observational period
Corticosteroid – nasal/ocular	Permitted	Permitted	Permitted
Corticosteroid – oral, inhaled*	Permitted†	Permitted (stable dose)‡	Permitted
Corticosteroid – i.v., i.m.	Permitted†	Not permitted‡	Permitted
SABA – inhaled§	Permitted†	Permitted (stable dose)‡	Permitted
LABA – inhaled§	Permitted†	Permitted (stable dose)‡	Permitted
SAMA – inhaled	Permitted†	Permitted (stable dose)‡	Permitted
LAMA – inhaled§	Permitted†	Permitted (stable dose)‡	Permitted
Leukotriene modifier	Permitted†	Permitted (stable dose)‡	Permitted
Cromolyn sodium / nedocromil sodium	Permitted†	Permitted (stable dose)‡	Permitted
Methylxanthines	Not permitted‖	Not permitted	Permitted
PDE-4 inhibitors	Not permitted‖	Not permitted	Permitted

Immunomodulators (e.g. methotrexate)	Not permitted‖	Not permitted	Permitted
Immunotherapy (e.g. subcutaneous or sublingual)	Permitted†	Permitted	Permitted
Biologic antagonists (e.g. omalizumab)	Not permitted‖	Not permitted	Not permitted
A1AT augmentation therapy	Not permitted	Not permitted	Permitted
Other investigational drugs	Not permitted	Not permitted	Not permitted

*For patients taking stable maintenance OCS with a total daily dose of ≤20 mg prednisone or equivalent.

†Allowed as stable dose for at least 4 weeks before Visit 1.

‡If unstable (e.g. in case of exacerbations), extend screening period.

§Includes fixed dose combination therapy.

‖Allowed before Visit 1 with a washout period of 3 months or 6 half-lives whichever is greater.

A1AT, alpha1-antitrypsin; LABA, long-acting β2-adrenergic agonist; LAMA, long-acting anticholinergic; OCS, oral corticosteroids; PDE-4, phosphodiesterase-4; SABA, short-acting β2-adrenergic agonist; SAMA, short-acting anticholinergic.

Supplementary table 5. Steering committee members

Scientific expert	Affiliation	Role
Prof. James Crapo	National Jewish Health, Denver (CO), USA	Chair/Advisor/Discussant
Prof. David Lynch	National Jewish Health, Denver (CO), USA	Advisor/Discussant
Dr. Henrik Watz	Pulmonary Research Institute, Lungen Clinic Grosshansdorf GmbH, Grosshansdorf, Germany	Advisor/Discussant
Prof. Pascal Chanez	CHU Marseille – Hôpital Nord, Marseille, France	Advisor/Discussant
Prof. Gaetan Deslee	CHU Reims – Hôpital Maison Blanche, Reims, France	Advisor/Discussant
Dr. Alice Turner	Centre for Translational Inflammation Research, Birmingham, UK	Advisor/Discussant
Dr. Richard Casaburi	Los Angeles Biomedical Research Institute, Torrance (CA), USA	Advisor/Discussant
Prof. Kazuhisa Asai	Osaka University Graduate School of Medicine, Osaka, Japan	Advisor/Discussant
Dr. Harald Koegler	Boehringer Ingelheim	Medical Project Lead
Dr. Markus Beck	Boehringer Ingelheim	Participant/Discussant
Dr. Claudia Diefenbach	Boehringer Ingelheim	Participant/Discussant
Dr. Frank Risse	Boehringer Ingelheim	Participant/Discussant
Dr Abhya Gupta	Boehringer Ingelheim	Participant/Discussant

Supplementary table 6. CT scan protocol in inspiration and expiration

Scan coverage	Lung apices to costophrenic recesses
Scanning mode	Helical
Scanning plane	Axial
Dose modulation	On
Detector configuration	64 x 0.625 mm (GE VCT Discovery STE, VCT Discovery 750HD 64 slice) 64 x 0.5 mm (Philips Brilliance 64 slice) (64)32 x 0.6 mm (Siemens Definition DS, Sensation 64 slice) (128)64 x 0.6 mm (Siemens Definition Edge, AS+ 128 slice, Flash 128 slice, Somatom Force)
kVp	120 kVp
mA/mAs	GE (750HD, Discovery STE): Target noise index: 66.5, Maximum mA limit 100 Philips (Brilliance 64): Reference mAs – 46 mAs (128 mA) Siemens (effective mA): Sensation 64, Definition (DS/AS 64 slice)/(AS+ 128 slice/Flash 128 slice), Edge, Force – Reference mAs 35 mAs
Pitch	GE (Discovery 750HD, Discovery STE) – 0.984 Philips (Brilliance 64) – 0.923 Siemens – 1.0
Rotation time	0.5 s
Reconstructions	
Non-iterative	GE (750HD, Discovery STE): Standard, Bone Philips (Brilliance 64): B, D (YB)

	Siemens (Sensation 64, Definition DS/AS/AS+/Flash 64/128): B31f, B45f (B46f) Siemens (Somatom Force): Bf40d, Qr44d Siemens (Somatom Definition Edge): Bf37f, Bv45f
Iterative	GE (750HD, Discovery STE): Standard ASIR 40%, Bone ASIR 40%, Standard ASIR 100% Philips (Brilliance 64): B iDose L3, D (YB) iDose L3, B iDose L7 Siemens (Sensation 64, Definition DS/AS/AS+/Flash 64/128): I31f SAFIRE 2, I44f SAFIRE 2, I31f SAFIRE 5 Siemens (Somatom Force): Bf40d ADMIRE 2, Qr44d ADMIRE 2, Bf40d ADMIRE 5 Siemens (Somatom Definition Edge): Bf37 f2, Br54 f2, Bf37 f5
Thickness	GE (Discovery 750HD, Discovery STE) – 0.625 Philips (Brilliance 64) – 0.67 Siemens – 0.75 mm
Interval	0.5 mm
DFOV	Lungs (no more than a 1 cm margin outside of the lungs on either side of the scan, where the lungs are the widest in the chest)
HD mode	GE (750HD, Discovery STE): OFF Philips (Brilliance 64): n/a Siemens (Sensation 64, Definition Edge/DS/AS/AS+/Flash 64/128, Somatom Force): n/a

DFOV, display field of view; HD, high definition.

References

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2. Bhatt SP, Bodduluri S, Hoffman EA*, et al.* Computed tomography measure of lung at risk and lung function decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196(5):569-76.
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4. Dirksen A, Piitulainen E, Parr D*, et al.* Exploring the role of CT densitometry: a randomised study of augmentation therapy in α1-antitrypsin deficiency. *Eur Respir J* 2009;33(6):1345-53.