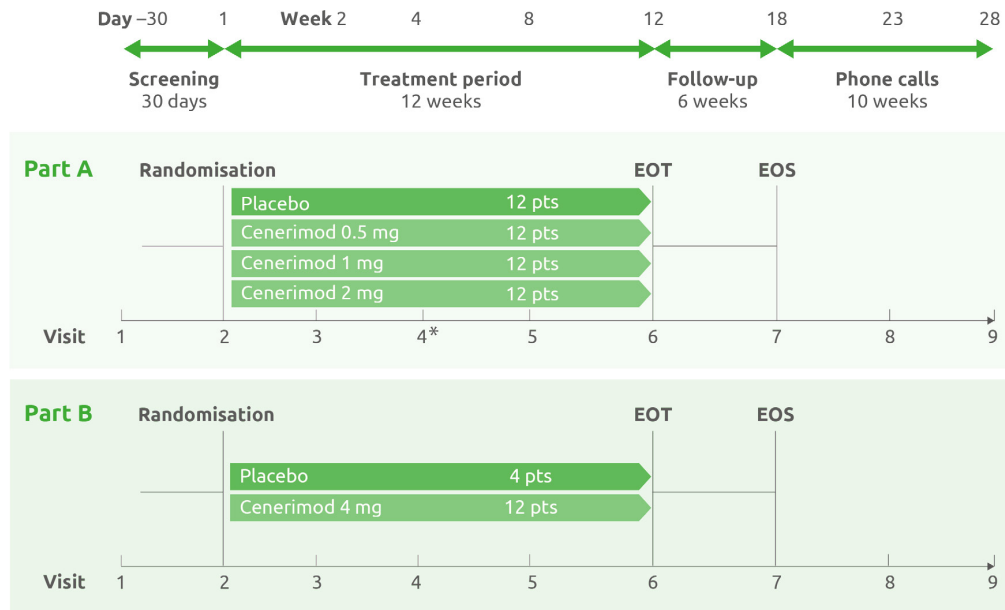


## Supplementary materials

### Supplementary file 1

#### Study design



Study design of part A and part B, with the sample sizes needed to provide an average power of at least 90%.

\*Safety interim review (Independent Data Monitoring Committee) done after 4 weeks of treatment in part A.

EOS, end of study; EOT, end of treatment; pts, patients.



## Supplementary file 2

### Inclusion and exclusion criteria

#### Additional inclusion criteria:

1. Women of childbearing potential:
  - a. Were required to have a negative serum pregnancy test at screening and a negative urine pregnancy test at randomisation; these pregnancy tests were required to be at least 3 weeks apart.
  - b. Agreed to perform a urine pregnancy test (bi-weekly/monthly) during the study and up to 16 weeks after study treatment discontinuation.
  - c. Were required to use approved methods of contraception from the screening visit up to 16 weeks after study treatment discontinuation.

#### Additional exclusion criteria:

##### *Cardiovascular*

1. History or presence of cardiac rhythm disorders (eg, sinoatrial heart block, second or third-degree atrioventricular block, symptomatic bradycardia, atrial flutter or atrial fibrillation, ventricular arrhythmias, cardiac arrest).
2. Resting heart rate <55 beats per minute as measured by the pre-dose 12-lead electrocardiogram (ECG) on day 1; a QT interval corrected for heart rate on the basis of Fridericia's formula of >470 ms (females) or >450 ms (males) at screening or on the day-1 ECG prior to study treatment initiation.
3. History or presence of ischaemic heart disease.
4. History or presence of myocarditis or endocarditis.
5. Presence of valvular heart disease associated with symptoms or haemodynamic change.
6. History of syncope associated with cardiac disorders.
7. History or presence of cardiac failure.
8. Systemic arterial hypertension not controlled by medication according to the investigator's judgment.
9. History or presence of vascular thrombosis at any time or a history of pregnancy morbidity in the context of anti-phospholipid antibody syndrome within 5 years prior to randomisation.
10. Clinically relevant hypotension according to the investigator's judgment or orthostatic hypotension (i.e., >20 mmHg decrease in systolic blood pressure or >10 mmHg decrease in diastolic blood pressure from supine to standing position measured between 1–3 minutes after standing) at screening.
11. Known pulmonary arterial hypertension of functional class III or IV.

##### *Pulmonary*

1. History or presence of severe respiratory disease or pulmonary fibrosis, based on medical history, lung function, and chest X-ray performed at screening or within 3 months prior to screening.
2. Bronchial asthma or chronic obstructive pulmonary disease.
3. Abnormal pulmonary function tests: forced expiratory volume in 1 second (FEV<sub>1</sub>) or forced vital capacity (FVC) <70% of predicted normal values; FEV<sub>1</sub>/FVC ratio <0.7.

##### *Treatments*

1. Treatment or planned treatment with any of the following medications:
  - a. Within 15 days or 5 half-lives of the medication, whichever was longer, prior to randomisation:
    - i.  $\beta$ -blockers, diltiazem, verapamil, digoxin or any other anti-arrhythmic or HR-lowering systemic therapy.
    - ii. QT-prolonging drugs with known risk of torsades de pointes, for any indication.
    - iii. Short- and long-acting  $\beta$ 2-agonists (eg, albuterol, levalbuterol, formoterol, terbutaline salmeterol)
  - b. Within 30 days or 5 half-lives of the medication, whichever was longer, prior to randomisation:
    - i. Cyclophosphamide, cyclosporine, tacrolimus, sirolimus, etc.
    - ii. Pulse methylprednisolone.
    - iii. Vaccination with live vaccines.

## Clinical trials and drug discovery

- c. Within 90 days prior to randomisation:
  - i. Belimumab, leflunomide.
  - ii. Any investigational immunosuppressive or immunomodulatory agent (within 90 days or 5 half-lives of the drug prior to start of study treatment, whichever was longer).
- d. Within 12 months prior to randomisation:
  - i. B cell-depleting biological agents such as rituximab or ocrelizumab.
- e. Any time prior to randomisation:
  - i. Alemtuzumab, sphingosine1-phosphate (S1P) receptor modulators (eg, fingolimod).

*Infection and infection risk*

1. Active or latent tuberculosis.
2. A history of any serious infection (ongoing known bacterial, viral or fungal infection).
3. Hepatitis B, Hepatitis C, congenital or acquired severe immunodeficiency or known human immunodeficiency virus (HIV) infection or positive HIV testing at screening.
4. Negative antibody test for varicella-zoster virus at screening.

*Malignancy*

1. History or presence of malignancy (except for surgically excised basal or squamous cell skin lesions), lymphoproliferative disease, or history of total lymphoid irradiation.

*Transplantation*

1. History or presence of bone marrow or solid organ transplantation.

*Ophthalmology*

1. Presence of macular oedema or active uveitis.

*Metabolic and hepatic*

1. Type-1 or -2 diabetes that was poorly controlled according to investigator's judgment or diabetes complicated with organ involvement such as diabetic nephropathy or retinopathy.
2. Moderate or severe hepatic impairment, defined by Child Pugh Score B or C, respectively.
3. Total bilirubin >1.5-fold the upper limit of normal, unless in the context of known Gilbert's Syndrome.
4. Alanine or aspartate aminotransferase >2-fold upper limit of normal.

*Haematology*

1. Haemoglobin <9 g/dL.
2. White blood cell <2500/ $\mu$ L ( $2.5 \times 10^9$ /L).
3. Lymphocyte count <800 / $\mu$ L ( $0.8 \times 10^9$ /L).
4. Platelets <75,000/ $\mu$ L ( $75 \times 10^9$ /L).

*Renal*

1. Proteinuria >1.0 g/24 h or equivalent, using spot urine protein-to-creatinine ratio.
2. Estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

*Other categories*

1. Pregnant, or planned to become pregnant, or breastfeeding.
2. History of clinically significant drug or alcohol abuse.
3. Known allergy to S1P<sub>1</sub> modulators or any of the cenerimod formulation excipients.
4. Any other clinically relevant medical or surgical condition that in the opinion of the investigator would have put the subject at risk if he/she participated in the study.
5. Unlikely to comply with the protocol.



### Supplementary file 3

#### Stopping criteria for events in safety areas of interest

Safety area of interest	Specific study stopping criteria being applied to stop subject/study
Cardiovascular	<ul style="list-style-type: none"> <li>HR &lt;40 bpm at 2 consecutive hourly 12-lead ECG post dose (day 1)</li> <li>SBP &lt;90 mmHg at 2 consecutive hourly blood pressure measurements post dose (day 1)</li> <li>Subject not meeting criteria for discharge from the hospital (day 1)</li> <li>QTcF &gt;500ms at any time as documented by 12-lead ECG</li> <li>Symptomatic bradycardia or hypotension (eg, syncope)</li> </ul>
Immune system and infections	<ul style="list-style-type: none"> <li>Confirmed total lymphocyte count &lt;200 cells/<math>\mu</math>L</li> <li>Clinically relevant infection (eg, serious infection, opportunistic infection)</li> </ul>
Respiratory systems	<ul style="list-style-type: none"> <li>FEV<sub>1</sub> and/or FVC &gt;15% decrease from the study baseline values which has been confirmed at repeat testing</li> <li>Persistent respiratory AEs (eg, dyspnoea)</li> </ul>
Liver	<ul style="list-style-type: none"> <li>Abnormal LTs or signs and symptoms suggestive of drug-induced liver injury</li> </ul>
Ocular	<ul style="list-style-type: none"> <li>Macular oedema confirmed by OSB</li> </ul>

AE, adverse event; bpm, beats per minute; ECG, electrocardiogram; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; LT, liver test; OSB, Ophthalmology Safety Board; QTcF, QT corrected for heart rate on the basis of Fridericia's formula; SBP, systolic blood pressure.

### Supplementary file 4

#### Adverse events of special interest

- Effect on heart rate and rhythm (including hypotension)
- Cardiovascular
- Hypertension
- Liver (hepatobiliary disorders/liver enzyme abnormality)
- Pulmonary
- Macular oedema
- Serious or severe infection
- Herpetic infection
- Skin malignancy
- Non-skin malignancy
- Stroke
- Seizure

#### Additional safety endpoints

The treatment-emergent period was defined as the time from the first study treatment intake up to 6 weeks (inclusive) after the last study treatment intake.

- Changes in 12-lead electrocardiogram (ECG) variables (heart rate, PR, QRS, QT, QT corrected for heart rate on the basis of Bazett's formula and QT corrected for heart rate on the basis of Fridericia's formula), from pre-dose to selected post-dose assessments (1, 2, 3, 4, 5, and 6 h) on day 1.
- Occurrence of treatment-emergent 12-lead ECG outliers.
- Occurrence of treatment-emergent 12-lead ECG abnormalities.
- Occurrence of treatment-emergent 24-hour Holter ECG abnormalities on day 1.
- Change in systolic blood pressure and diastolic blood pressure from baseline to each post-baseline assessment up to end of the study (EOS).
- Changes in forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC), expressed in absolute value and percent value from baseline to each post-baseline assessment up to EOS.
- Occurrence of treatment-emergent decrease of FEV<sub>1</sub> and FVC >15% from baseline values.
- Changes in laboratory variables (haematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment up to EOS.
- Treatment-emergent laboratory abnormalities according to the Common Terminology Criteria for Adverse Events 2010 v4.03
- Change in protein-to-creatinine ratio from baseline to end of treatment (EOT).
- Change in body weight from baseline to EOT.

## Clinical trials and drug discovery

## Supplementary file 5

## Additional exploratory endpoints

*Pharmacokinetic endpoints*

- Plasma cenerimod concentrations at trough prior to dosing at weeks 2, 4, and 8 and at week 12/end of treatment (EOT) or the EOT visit after premature study treatment discontinuation (if applicable).
- Plasma cenerimod concentration at end of study (i.e., 6 weeks after study treatment discontinuation).

*Exploratory disease activity endpoints*

- Change in Physician's Global Assessment score from baseline to each post-baseline assessment.

*Quality of life endpoints*

- Change in SF-36v2 Health Survey domain and component scores from baseline to EOT.

*Exploratory biomarker endpoints*

- Changes in serum levels of immunoglobulin (Ig)G, IgM, and IgA from baseline to each post-baseline assessment.
- Changes in serum complement components C3 and C4, C-reactive protein, fibrinogen, B lymphocyte stimulator, and C-X-C motif chemokine ligand 10 from baseline to each post-baseline assessment.

## Supplementary file 6

## Modified SLEDAI-2K scores by treatment group

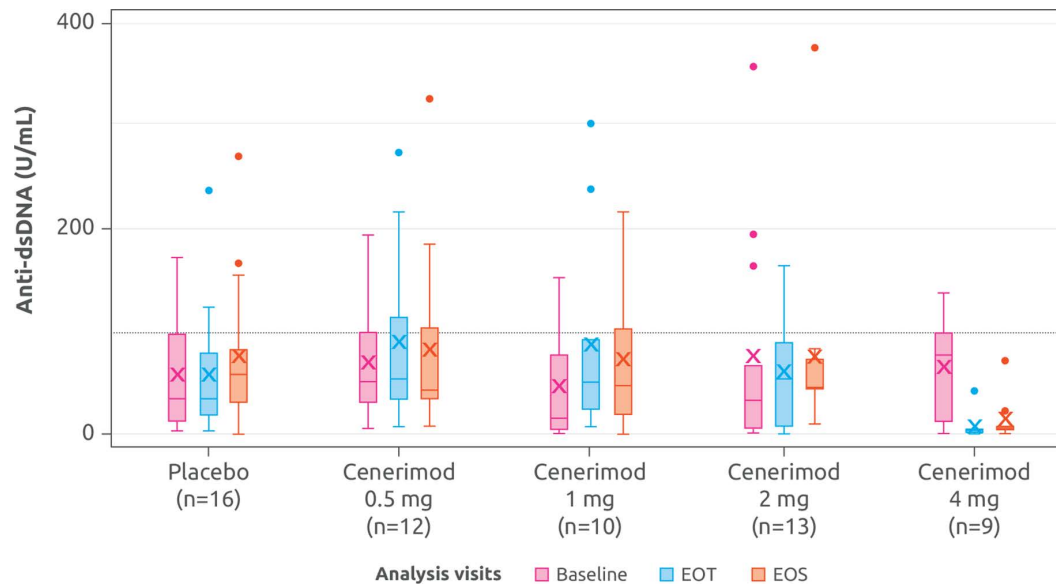
	Placebo (n=16)	Cenerimod			
		0.5 mg (n=12)	1 mg (n=10)	2 mg (n=13)	4 mg (n=9)
<b>mSLEDAI-2K score at baseline (mean ± SD)</b>	7.31 ± 3.36	7.25 ± 3.33	7.00 ± 2.16	7.08 ± 2.25	8.11 ± 2.47
<b>mSLEDAI-2K score at EOT (mean ± SD)</b>	5.38 ± 3.07	6.25 ± 3.08	6.00 ± 2.67	4.77 ± 3.00	3.33 ± 2.45
<b>Absolute change from baseline to EOT (mean ± SD)</b>	-1.94 ± 2.54	-1.00 ± 3.77	-1.00 ± 2.36	-2.31 ± 2.93	-4.78 ± 3.23
<b>Treatment difference compared with placebo</b>					
<b>Estimate (SE)</b>	-	0.91 (1.00)	0.77 (1.05)	-0.49 (0.97)	-2.42 (1.09)
<b>P-value</b>	-	0.3673	0.4652	0.6138	0.0306

Treatment difference in mSLEDAI-2K scores were analysed based on pairwise comparisons of the reduction in mSLEDAI-2K score from baseline for each cenerimod dose level to placebo using an analysis of covariance (ANCOVA) model. Modified PD set (n=60). EOT, end of treatment; PD, pharmacodynamic; SD, standard deviation; SE, standard error; mSLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000, modified to exclude leucopenia.



## Supplementary file 7

Anti-dsDNA values at baseline, EOT, and EOS, by treatment group

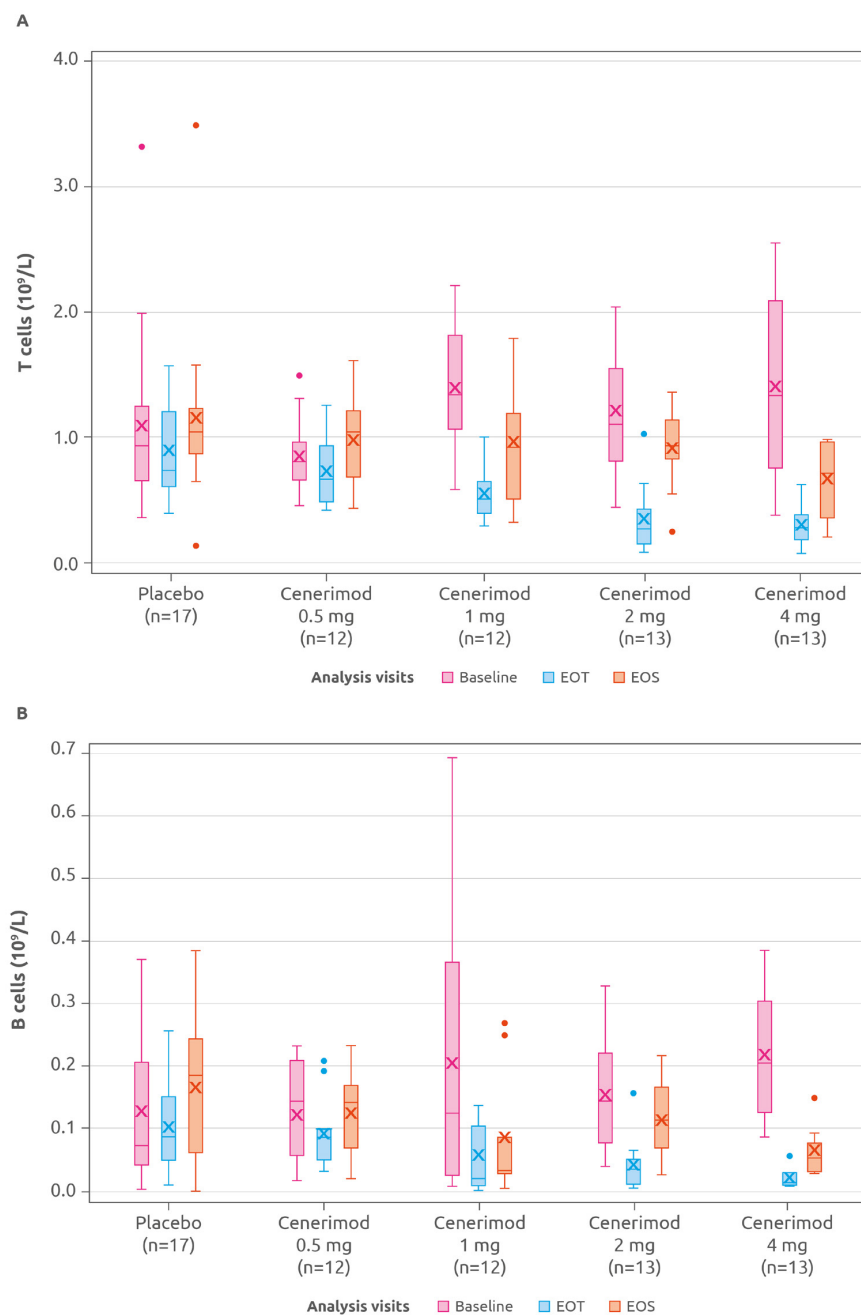


Anti-dsDNA, biomarker for SLE, detected in peripheral blood. Box and whisker plots indicate the interquartile range (box), upper and lower 1.5 interquartile range (whiskers), mean and median (cross and horizontal line, respectively, within the box), and outliers at least above or below 1.5 times the interquartile range (dots). mPD analysis set (n=60).

dsDNA, double-stranded deoxyribonucleic acid; EOS, end of study; EOT, end of treatment; mPD, modified pharmacodynamics.

## Supplementary file 8

T and B lymphocyte count in peripheral blood at baseline, EOT, and EOS, by treatment group



(A) Total T lymphocyte count in peripheral blood; (B) total B lymphocyte count in peripheral blood.

Box and whisker plots indicate the interquartile range (box), upper and lower 1.5 interquartile range (whiskers), mean and median (cross and horizontal line, respectively), within the box, and outliers at least above or below 1.5 times the interquartile range (dots). Full analysis set (N=67). EOS, end of study; EOT, end of treatment.



## Supplementary file 9

Treatment-emergent AEs of special interest

Patients n (%)	Placebo (n=17)	Cenerimod				Total (N=67)
		0.5 mg (n=12)	1 mg (n=12)	2 mg (n=13)	4 mg (n=13)	
<b>Liver AEs of special interest</b>						
Subjects with $\geq 1$ AE	1 (5.9)	2 (16.7)	-	1 (7.7)	1 (7.7)	5 (7.5)
Blood ALP increase	-	-	-	-	1 (7.7)	1 (1.5)
Chronic hepatitis	-	-	-	-	1 (7.7)	1 (1.5)
ALT increase	-	2 (16.7)	-	-	-	2 (3.0)
AST increase	-	1 (8.3)	-	-	-	1 (1.5)
Bilirubin conjugated increase	-	1 (8.3)	-	1 (7.7)	-	2 (3.0)
Blood bilirubin increase	-	-	-	1 (7.7)	-	1 (1.5)
Blood fibrinogen decrease	1 (5.9)	-	-	-	-	1 (1.5)
<b>Pulmonary AEs of special interest</b>						
Patients with $\geq 1$ AE	-	-	1 (8.3)	-	-	1 (1.5)
Pneumonitis	-	-	1 (8.3)	-	-	1 (1.5)

AEs by preferred term. Safety set (N=67).

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

## Supplementary file 10

Absolute change in spirometry values from baseline to EOT

Spirometry variable	Placebo (n=17)*	Cenerimod			
		0.5 mg (n=12)	1 mg (n=12)	2 mg (n=13)	4 mg (n=13)
<b>FEV<sub>1</sub> (L)</b>					
Median	0.00	-0.11	-0.09	-0.17	-0.10
Mean $\pm$ SD	0.004 $\pm$ 0.297	-0.103 $\pm$ 0.171	-0.117 $\pm$ 0.213	-0.177 $\pm$ 0.147	-0.115 $\pm$ 0.264
<b>FVC (L)</b>					
Median	-0.06	-0.12	-0.13	-0.15	-0.13
Mean $\pm$ SD	-0.055 $\pm$ 0.246	-0.173 $\pm$ 0.298	-0.092 $\pm$ 0.289	-0.109 $\pm$ 0.131	-0.148 $\pm$ 0.413
<b>FEV<sub>1</sub> (% predicted)</b>					
Median	-0.046	-3.532	-3.017	-6.013	-4.712
Mean $\pm$ SD	0.485 $\pm$ 10.293	-3.818 $\pm$ 6.117	-4.154 $\pm$ 7.677	-5.766 $\pm$ 4.644	-3.373 $\pm$ 8.831
<b>FVC (% predicted)</b>					
Median	-1.924	-3.693	-3.998	-3.658	-4.370
Mean $\pm$ SD	-1.413 $\pm$ 7.469	-5.314 $\pm$ 8.983	-2.666 $\pm$ 8.909	-3.063 $\pm$ 3.830	-3.345 $\pm$ 11.185
<b>FEV<sub>1</sub>/FVC</b>					
Median	0.010	0.008	-0.016	-0.031	0.005
Mean $\pm$ SD	0.012 $\pm$ 0.032	0.003 $\pm$ 0.041	-0.019 $\pm$ 0.052	-0.026 $\pm$ 0.031	-0.002 $\pm$ 0.038
<b>Peak expiratory flow (L/s)</b>					
Median	-0.37	-0.40	-0.24	-0.08	-0.43
Mean $\pm$ SD	-0.379 $\pm$ 0.720	-0.139 $\pm$ 0.720	-0.219 $\pm$ 0.418	-0.285 $\pm$ 0.560	-0.449 $\pm$ 0.419
<b>FEF<sub>25-75%</sub> (L/s)</b>					
Median	0.023	-0.183	-0.291	-0.419	-0.098
Mean $\pm$ SD	0.114 $\pm$ 0.708	-0.086 $\pm$ 0.441	-0.245 $\pm$ 0.457	-0.446 $\pm$ 0.506	-0.103 $\pm$ 0.396

\*n=16 as spirometry assessment data is not available for one patient.

Safety set (N=67).

EOT, end of treatment; FEF, forced expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 second, FVC, forced vital capacity; SD, standard deviation.