Efficacy of Roflumilast in Bronchiectasis Patients with Frequent Exacerbations: A Double-Blinded, Randomized, Placebo-Controlled Pilot Clinical Trial

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Running title: efficacy of roflumilast in bronchiectasis

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Data curation: Siwasak Juthong and Pattaraporn Panyarath
Software: Siwasak Juthong
Validation: Siwasak Juthong and Pattaraporn Panyarath
Investigation: Siwasak Juthong and Pattaraporn Panyarath

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Writing - review and editing: Siwasak Juthong and Pattaraporn Panyarath

Approval of final manuscript: all authors.

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Efficacy of Roflumilast in Bronchiectasis Patients with Frequent Exacerbations: A Double-Blinded, Randomized, Placebo-Controlled Pilot Clinical Trial

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Abstract

Background: Bronchiectasis patients with neutrophilic airway inflammation develop symptoms of chronic cough, sputum production, and recurrent exacerbations. Roflumilast has anti-inflammatory actions via decreased neutrophilic airway inflammation. The effectiveness of roflumilast to reduce bronchiectasis exacerbation has never been evaluated.

Methods: We conducted a double-blind, randomized, placebo-controlled trial. The primary objective was to assess the effect of roflumilast compared with placebo to reduce exacerbation rates in bronchiectasis patients. The secondary objectives were the changes in FEV₁ and SGRQ. Bronchiectasis patients older than 18 years and had two exacerbations during the previous 12 months were randomly assigned to receive either 500 µg of roflumilast or placebo once daily for 6 months in a 1:1 ratio.

Results: Forty bronchiectasis patients who experienced exacerbations were screened. Thirty patients completed the study after 6 months of treatment: roflumilast group (n=15) and placebo group (n=15). The rates of exacerbations were 0.57 and 0.59 per patient in the roflumilast and placebo groups, respectively. Pre-bronchodilator FEV₁ increased by 0.07 liter from baseline in the roflumilast group and decreased by 0.015 liter in the placebo group but the difference was not significant. No significant differences were observed in the change of
SGRQ scores between the roflumilast and placebo groups. Roflumilast had significant side effects including loss of appetite and headache.

**Conclusions:** Roflumilast did not significantly affect the rate of exacerbations and quality of life. However, FEV$_1$ tended to improve in the roflumilast group compared with the placebo group.

**Keywords:** Bronchiectasis; Exacerbations; Lung functions; Roflumilast

Clinical trial registration: NCT 04122547 at ClinicalTrials.gov

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**Introduction**

Bronchiectasis patients have clinical symptoms of chronic cough, productive sputum, hemoptysis, recurrent pulmonary exacerbations, and frequent hospitalization resulting in dyspnea, low quality of life, and high mortality\(^1\). Bronchiectasis is a chronic neutrophilic airway inflammation\(^2\). Neutrophils are key components of lung damage and dilated bronchi\(^3,4\).
Bronchiectasis is characterized by a vicious cycle of airway inflammation, poor mucus clearance, bacterial colonization, airway obstruction, and progressive tissue destruction. The strategy is to break the vicious cycle to improve patient outcomes. The goals of therapeutic approaches are management of chronic bacterial infections and prevention of exacerbations.

Pulmonary exacerbations of bronchiectasis are defined by an increase in daily respiratory symptoms such as cough, sputum production, breathlessness, malaise, and fatigue. Bronchiectasis patients with frequent exacerbations have a low quality of life and increased mortality. The European Respiratory Society and British Thoracic Society bronchiectasis guidelines emphasize exacerbation prevention and improvement in the symptoms and quality of life of the patients.

The chronic bronchitis component of bronchiectasis is a shared common mechanism in chronic obstructive pulmonary disease (COPD). Roflumilast is an anti-inflammatory agent and inhibitor of phosphodiesterase 4 that significantly reduces exacerbations in COPD with chronic bronchitis and a high baseline frequency of exacerbations. The anti-inflammatory actions of roflumilast are an increase in the cyclic adenosine monophosphate level and decreased neutrophil-driven airway inflammation, reduced neutrophil chemotaxis, decreased release of pro-inflammatory mediators, and induction of neutrophil apoptosis. Therefore, it is logical to consider roflumilast for the treatment of bronchiectasis.

Park reported a phase II trial using roflumilast 250 µg or 500 µg for a 16-week duration in nine symptomatic bronchiectasis patients. The participants had improved health-related quality of life measured by the COPD assessment test score and the St George’s Respiratory Questionnaire (SGRQ) but the results did not achieve statistical significance. The study did not report on exacerbations or lung function tests which would be the most important clinical trial end-points for bronchiectasis patients. To date, no study has reported on roflumilast to reduce exacerbations or the performance of lung function tests in bronchiectasis patients.
frequent exacerbations. We did a study to determine the effect of roflumilast on the exacerbation of bronchiectasis.

**Materials and Methods**

1. **Study design and patients**

   A prospective preliminary double-blind, randomized, placebo-controlled trial was conducted in Songklanagarind Hospital, Thailand from January 2015 to November 2015. The participants included: 1) bronchiectasis patients older than 18 years at the outpatient department and diagnosed as bronchiectasis by high-resolution computed tomography (HRCT) and 2) bronchiectasis patients who had a history of exacerbation equal to or more than 2 times in the previous 12 months. The exacerbation of bronchiectasis was defined as patients who had at least three of these symptoms: increased cough, sputum production, change in sputum color, breathlessness, or hemoptysis and the doctor prescribed antibiotics.

   The exclusion criteria were: 1) patients diagnosed as COPD, active tuberculosis or interstitial lung disease, or lung cancer; 2) cirrhosis or psychiatric disease; 3) smoking history of more than 15 pack-years; 4) previous use of systemic antibiotics or theophylline therapy within 30 days before study entry; 5) patients in lactation period; 6) body weight less than 30 kg; and 7) patients who had contraindications to perform spirometry or the 6MWT. This study was approved by the Office of Human Research Ethics Committee at the Faculty of Medicine, Prince of Songkla University, Thailand. The Ethics Committee approval number was EC 57-261-14-4 dated 23 February 2015. This study was supported by institutional funding. We followed the CONSORT 2010 statement from www.consort-statement.org.

2. **Study objectives**

   The primary objective of this study was to compare exacerbation rates in bronchiectasis patients who received roflumilast or placebo during a 6-month follow-up period. The
secondary objectives were to describe patient-reported outcomes between patients who received roflumilast or placebo based on the results of FEV$_1$, SGRQ, and the 6MWT.

3. Sample size

This study was a pilot phase III double-blinded, randomized, placebo-controlled clinical trial. Forty bronchiectasis patients were screened and 15 patients were randomized into each group (total sample=30).

4. Study drugs and measurements

Roflumilast (Daxas®) 500 μg tablets were manufactured by Takeda Pharmaceutical Company. Placebo tablets were manufactured by the Department of Pharmaceutical Manufacturing, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand. All patients included in the study met the inclusion criteria and signed informed consent forms. They were then computer randomized 1:1 with block of four to receive either once daily roflumilast 500 μg or placebo for 24 weeks. All patient baseline characteristics that were recorded included smoking status, current and past chest symptoms, possible etiology of bronchiectasis, concurrent respiratory medications, history of vaccinations, pulmonary rehabilitation, and history of previous bronchiectasis exacerbations in the previous 12 months. Data recorded at the first visit and at the 24-week visit at the end of the study protocol included the SGRQ, pulmonary function tests (i.e., FEV$_1$, forced vital capacity [FVC]), 6MWT, and diffusing capacity for carbon monoxide.

5. Study protocol

All participants signed the informed consent forms and all patients continued to use the previous baseline standard treatments. They were then randomized to receive either once
daily roflumilast 500 μg or placebo for 24 weeks. The patients had scheduled visits every 4
weeks for the surveillance of acute exacerbation and the potential for adverse drug effects. If
the patients had an exacerbation of bronchiectasis, they were treated with the appropriate
antibiotic for 10 days. Sputum cultures for aerobic bacteria were performed at the first visit
and at the end of the study protocol. All participants were informed of pulmonary
rehabilitation (e.g., breathing exercise and postural drainage) and they continued to use prior
medications.

6. Statistical analysis

Since our clinical trial was a pilot study, we did not perform a sample size calculation.
Therefore, the limited number of samples possibly affected the statistical significance of this
study. We used the Stata version 14 program for the analysis. Continuous variables
demographic data) are presented as mean±SD and were compared using the Student t-test.
Non-continuous variables are presented as number and percentage which were compared
using the chi-square and Fisher’s exact tests. A Kaplan-Meier estimation curve and Cox’s
proportional hazards model were used to determine the first exacerbation. The Poisson
regression model was used for the rate of event-based exacerbations per patient. A two-tailed
p-value <0.05 was considered statistically significant. We analyzed the outcomes as per
protocol analysis.

Results

1. Demographics of patients

Forty bronchiectasis patients confirmed by HRCT were screened. Initially, the patients
were randomized into the treatment group (n=17) and control group (n=17). However, 15
patients in each group completed the study. Two patients in the roflumilast group and 2
patients in the placebo group dropped out at week 1 due to adverse effect intolerance. Finally, 15 patients each in the treatment and control groups continued until the end of the study (Figure 1). Demographic and clinical characteristics at the time of study entry are presented in Table 1. The median ages were 56.6±10.4 and 57.0±9.3 years for the bronchiectasis group and placebo group, respectively. Twenty-two (73.3%) patients were women and the mean age was 57 years. The mean number of exacerbations in the previous year before study entry were 4.2±2.85 and 3.1±1.95 times for the bronchiectasis and placebo groups, respectively (p=0.21). There were no differences in the baseline characteristics between the two groups such as body mass index, FEV₁, FVC, FEV₁/FVC, history of previous respiratory drug use, vaccination, 6MWT, and modified Medical Research Council dyspnea scale (Table 1). At baseline, the roflumilast group had total SGRQ scores higher than the placebo group (49.0 points vs. 33.7 points) (p=0.02).

2. Exacerbations

After completion of the 6-month study, the numbers of exacerbations in the roflumilast and placebo groups were 12 and 13 times, respectively. The rates of event-based exacerbations in the roflumilast and placebo groups were 0.57 and 0.59 times/patient, respectively, which was not significantly different. The rate ratio was equal to 0.97 (95% confidence interval [CI] 0.28–3.04, p=0.96). The lengths of time to the first exacerbation were 9.3 weeks in the patients who received roflumilast and 10.1 weeks in the placebo group (p=0.92) (Figure 2).

3. Pulmonary function tests

After 6 months of roflumilast, the pre-bronchodilator FEV₁ increased 70 mL compared with a decrease of 15 mL in the placebo group but this was not significantly different.
(difference 85 mL, 95% CI −0.08–0.25, p=0.28). The pre-bronchodilator FVC decreased 10 mL in the roflumilast group and decreased 1 mL in the placebo group (difference 9 mL, 95% CI −0.19–0.16, p=0.88). The 6MWT increased 21.0 meters in the roflumilast group compared with an increase of 22.8 meters in the placebo group (difference −1.8 meters, 95% CI −66.9–63.2, p=0.95) (Table 2).

4. Health-related quality of life

Following the 6-month study period, the total scores of the SGRQ decreased 13.5 and 5.5 points in the roflumilast and placebo groups, respectively (difference −8 points, 95% CI −20.3–4.4, p=0.19). The SGRQ symptoms, activity, and impacts scores were not statistically significantly different between the roflumilast and placebo groups (Table 2).

5. Adverse events

There was a significantly greater number of bronchiectasis patients in the roflumilast group versus the placebo group who had adverse effects (9 vs. 2 patients, p=0.02). The most common side effects of roflumilast were loss of appetite or fatigue (46.7%), headache (33.3%), nausea or vomiting (26.7%), and diarrhea (13.3%) (Table 3). The severities of the adverse events were grade 1 and grade 2. Four patients quit the study drug or placebo: 2 in the roflumilast group due to nausea and 2 patients in the placebo group due to headache.

Body weight losses in the roflumilast and placebo groups were 1.37 kg and 0.77 kg, respectively, but did not reach statistical significance (p=0.61).

Adherence to the protocol was determined. It was found that the numbers of patients in the roflumilast and placebo groups who regularly used 80% of the total dose were 10 patients (66.7%) and 14 patients (93.3%), respectively (p=0.06).
Discussion

In the bronchiectasis patients who experienced frequent exacerbations, treatment with roflumilast 500 μg once daily for 6 months did not significantly reduce exacerbations compared with placebo. Roflumilast tended to improve FEV₁ but this was not statistically significant compared with placebo. The health-related quality of life and exercise capacity as assessed by the 6MWT were not significantly different between the two groups. The number of bronchiectasis patients who received roflumilast and had side effects, such as loss of appetite, fatigue, headache, nausea or vomiting and diarrhea, was significantly greater.

Roflumilast has anti-neutrophilic inflammatory effects and significantly decreases exacerbations in frequent exacerbators with the chronic bronchitis phenotype of COPD. In this study roflumilast did not significantly reduce the time to the first exacerbation or event rate exacerbation in bronchiectasis. Bronchiectasis has a more complicated pathophysiology in exacerbation, such as more bacterial colonization, structural abnormality, and abnormal mucus clearance, than COPD. Roflumilast inhibits inflammation but has no effect in reducing bacterial colonization or mucus clearance. Our pilot study had a low number of bronchiectasis patients. Therefore, a similar study may need a larger number of patients to determine how roflumilast affects the exacerbation rate. The side effects of roflumilast possibly affected adherence to the drug. The heterogeneity of bronchiectasis exacerbation is due to multiple mechanisms such as the infection or inflammatory process or both.

Roflumilast tended to improve FEV₁ compared with placebo. After 24 weeks of roflumilast therapy, the FEV₁ increased 70 mL in bronchiectasis patients which was similar to COPD patients who had an improvement in FEV₁ of 57 mL. The mechanism of an increased FEV₁ with roflumilast therapy is not fully understood. Roflumilast may inhibit neutrophilic airway inflammation that breaks the vicious cycle of infection and inflammation which affects the airway caliber. However, roflumilast was reported to have no
effect on airway smooth muscle relaxation. The structural change in bronchiectasis is considered to be irreversible; therefore, a drug which is able to increase FEV₁ may be interesting.

In this study, roflumilast improved the quality of life as assessed by the SGRQ with an 8-point difference after 6 months of therapy. Although the total scores of the SGRQ changed after treatment, they were not significantly different from the placebo group. However, the change met the minimal clinical important difference of 4 points in the total scores of the SGRQ. The improved quality of life by roflumilast was the same as a study by Park et al., in which roflumilast significantly improved the quality of life. In this study, roflumilast improved FEV₁ but did not improve the exercise capacity which would improve the symptoms of dyspnea and quality of life. The results of the 6MWD showed no significant difference between the roflumilast and placebo groups. This occurred possibly because the patients were less dyspneic based on the scores of the modified Medical Research Council scale which were mainly 1 and 2 in both groups.

In bronchiectasis patients, roflumilast had significantly more side effects than the placebo. These side effects were not serious adverse events and were not life threatening. The most common side effect of roflumilast in bronchiectasis was loss of appetite or fatigue compared with diarrhea in COPD patients. The roflumilast patients experienced a weight loss of 1.37 kg compared with 2.09 kg in a COPD study. Weight loss can affect the quality of life due to a lower body mass index in bronchiectasis patients.

This study has some strengths and limitations. The first strength is the study design which was the first randomized double-blind placebo-controlled trial of roflumilast in bronchiectasis patients. Second, we selected bronchiectasis patients with frequent exacerbations who had a high clinical burden and severe disease. Third, roflumilast was taken for a period of 6 months which could demonstrate its effects on exacerbation and patient-reported outcomes. The
limitations include the low number of bronchiectasis patients and the study was conducted at a single center.

Conclusions
In bronchiectasis patients with frequent exacerbations, roflumilast 500 μg daily for 6 months did not significantly affect the rate of exacerbations or quality of life compared with placebo. However, it tended to improve lung functions. Roflumilast tended to improve the symptoms and impacts of bronchiectasis in a very small group of subjects in a short study. A longer-term prospective study with a larger number of bronchiectasis patients should be conducted.

Acknowledgement
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Conflict of Interest
The authors declare that they have no conflict of interest

References


<table>
<thead>
<tr>
<th></th>
<th>Roflumilast (N=15)</th>
<th>Placebo (N=15)</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean±SD</strong></td>
<td>56.6±10.4</td>
<td>57.0±9.3</td>
<td>0.840</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>6 (40.0)</td>
<td>2 (13.3)</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td>0.042</td>
</tr>
<tr>
<td>Never smoking</td>
<td>10 (66.7)</td>
<td>15 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (6.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>History smoker</td>
<td>4 (26.7)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>1.4 (3.54)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>20.78</td>
<td>21.48</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>51.88 (7.03)</td>
<td>50.95 (12.31)</td>
<td>0.80 (−6.5–8.4)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>158.6 (8.86)</td>
<td>154.26 (8.48)</td>
<td>0.18 (−2.15–10.8)</td>
</tr>
<tr>
<td><strong>Exacerbations in past year</strong></td>
<td>4.2 (2.85)</td>
<td>3 (2.29)</td>
<td>0.21 (−0.74–3.14)</td>
</tr>
<tr>
<td><strong>Spirometry before bronchodilation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.48 (0.54)</td>
<td>1.15 (0.41)</td>
<td>0.07 (−0.37–0.68)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.16 (0.60)</td>
<td>1.75 (0.55)</td>
<td>0.06 (−0.2–0.84)</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>67.73 (13.44)</td>
<td>66.46 (11.47)</td>
<td>0.78 (−8.08–10.61)</td>
</tr>
<tr>
<td><strong>Total scores on St George’s respiratory questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>53.83 (24.98)</td>
<td>43.57 (24.38)</td>
<td>0.26 (−8.20–28.2)</td>
</tr>
<tr>
<td>Activity</td>
<td>54.20 (21.6)</td>
<td>41.25 (25.64)</td>
<td>0.14 (−4.79–30.6)</td>
</tr>
<tr>
<td>Impacts</td>
<td>44.51 (18.08)</td>
<td>26.75 (21.80)</td>
<td>0.02 (2.7–32.7)</td>
</tr>
<tr>
<td><strong>6-minute walk test distance (m), mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>422.6 (67.13)</td>
<td>410.06 (41.3)</td>
<td>0.56 (−29.6–53.69)</td>
</tr>
<tr>
<td><strong>Respiratory drugs</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Any</td>
<td>5 (33.3)</td>
<td>6 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Short acting β2 agonists</td>
<td>2 (13.3)</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Long acting β2 agonists</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid inhaled with LABA</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccination history in past year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>11 (73.3)</td>
<td>11 (73.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>8 (53.3)</td>
<td>6 (40.0)</td>
<td>0.710</td>
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<tr>
<td><strong>Pulmonary rehabilitation</strong></td>
<td>0</td>
<td>2 (13.3)</td>
<td>0.480</td>
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<tr>
<td><strong>mMRC dyspnea scale</strong></td>
<td></td>
<td></td>
<td>0.160</td>
</tr>
<tr>
<td>1</td>
<td>1 (6.7)</td>
<td>5 (33.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (86.7)</td>
<td>10 (66.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (6.7)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated.

SD: standard deviation; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; LABA: long-acting β2 agonist; mMRC: modified Medical Research Council.
Table 2. Patient-reported outcomes and changes from baseline at 6 months after initiation of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Change from baseline</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Roflumilast group (N=15)</td>
<td>Placebo group (N=15)</td>
<td></td>
</tr>
<tr>
<td>Prebronchodilator FEV₁ (L)</td>
<td>0.07</td>
<td>−0.015</td>
<td>−0.08−0.25</td>
</tr>
<tr>
<td>Prebronchodilator FVC (L)</td>
<td>−0.01</td>
<td>−0.01</td>
<td>−0.19−0.16</td>
</tr>
<tr>
<td>Prebronchodilator FEV₁/FVC (%)</td>
<td>1.4</td>
<td>−1.14</td>
<td>−0.12 to 5.2</td>
</tr>
<tr>
<td>Total Score on St George’s respiratory questionnaire</td>
<td>−13.46</td>
<td>−5.54</td>
<td>−20.27−4.41</td>
</tr>
<tr>
<td>Symptoms</td>
<td>−19.66</td>
<td>−8.23</td>
<td>−27.47−4.6</td>
</tr>
<tr>
<td>Activity</td>
<td>−8.19</td>
<td>−6.05</td>
<td>−20.25−15.96</td>
</tr>
<tr>
<td>Impacts</td>
<td>−16.52</td>
<td>−3.85</td>
<td>−27.65−2.32</td>
</tr>
<tr>
<td>6-minute walk test distance (m)</td>
<td>21</td>
<td>22.8</td>
<td>−66.93−63.22</td>
</tr>
</tbody>
</table>

*FEV₁*: forced expiratory volume in 1 second; FVC: forced vital capacity; CI: confidence interval.

Table 3. Adverse events from roflumilast and placebo.

<table>
<thead>
<tr>
<th></th>
<th>Roflumilast (N=15)</th>
<th>Placebo (N=15)</th>
<th>p-value (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Any adverse events</td>
<td>9 (60.0)</td>
<td>2 (13.3)</td>
<td>0.020</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>0.500</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>7 (46.7)</td>
<td>0 (0.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>4 (26.7)</td>
<td>0 (0.0)</td>
<td>0.050</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (33.3)</td>
<td>1 (6.7)</td>
<td>0.080</td>
</tr>
<tr>
<td>Body weight loss (kg)</td>
<td>−1.37 (2.7)</td>
<td>−0.77 (3.6)</td>
<td>0.61 (−3.02−1.82)</td>
</tr>
<tr>
<td>Compliance &gt;80.0% of total dose</td>
<td>10 (66.7)</td>
<td>14 (93.3)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated.

CI: confidence interval.
Figure 1. Patient flow diagram.

40 patients were screened

Excluded due to
Advanced cirrhosis (n=1)
Pregnancy (n=1)
Could not perform spirometry (n=2)
Declined to participate (n=2)

34 patients were assigned

Two patients dropped out due to side effects

Roflumilast group
n=15

Placebo group
n=15

Two patients dropped out due to side effects
Figure 2. Kaplan-Meier curve for the time of first exacerbation in bronchiectasis patients who received roflumilast and placebo.