Study Results

of Non-Interventional Study

Consolidated report
Analysis of all country data

Study ID:
RO-2455-407-RD

Title:
The PROFILE Study, <u>P</u>atient Registry of <u>ROF</u>lumilast <u>I</u>n <u>R</u>eal Lif<u>E</u>

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Contents

Introduction

This document contains the results of The PROFILE study for all participating European countries (Bulgaria, Germany, Greece, Norway and Slovakia). Tables and figures presented in this document are created according the final version of study protocol (Amendment 3 dated 17.9.2014 to the Protocol dated 24. 7. 2012) and the final version of Statistical Analysis Plan and table shells (Version 4, 24. 2. 2015).

Background

Roflumilast (Daxas®) is a novel oral therapy indicated for maintenance treatment of severe COPD (Forced Expiratory Volume in the first second (FEV1) post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add on to bronchodilator treatment. Several clinical trials have been conducted on the efficacy and safety of roflumilast (Daxas®) and the data from these trials has been widely published. This patient registry was designed to capture real life data and to demonstrate the performance of roflumilast (Daxas®) in standard clinical practice.

Methods

This observational, non-interventional, non-comparative, prospective study, to collect data on patients treated with Roflumilast (Daxas®) was conducted in in 5 European countries (Bulgaria, Germany, Greece, Norway and Slovakia). The design allowed for the collection of data without interfering with the treatment practices of the physicians involved in the data collection. Subjects were followed according to usual practice. Respecting standard clinical practice in each centre, data, if available, was recorded at approximately 3, 6, 9 and 12 months after start of roflumilast (Daxas®) treatment. The primary endpoint of the study was to document the incidence and frequency of exacerbations in patients with COPD during a one-year period of treatment with roflumilast (Daxas®).

Design limitations

Non-Interventional studies are designed to ensure data collection or patient-participation does not interfere with the physician's choice of treatment, sample collection and procedures. Collecting data while ensuring that the physician continues to treat patients according to standard of care does result in data limitations. The non-interventional design in addition to limiting the study to subjects being treated

with roflumilast (Daxas®) result in a number of limitations which include, but are not limited to, the following:

- The enrolment of patients in participating countries may have been influenced by availability of treatment and local guidelines for roflumilast (Daxas®) treatment resulting in different compositions of patients in participating countries.

- Comparison of retrospective and prospective data could be biased if the retrospective source data were incomplete and/or collected under conditions that differ from those for the prospective data.

- Concomitant therapy may have been influenced by national guidelines and local preferences of participating centers and thus led to differing structure of treatment regimens.

- During the study possible changes in guidelines for Rroflumilast (Daxas®) therapy or guidelines for concomitant therapy may have occurred.

- Standard monitoring was not carried out which may have an impact on the quality of data entered.

    o Proportion of incomplete data (either due to omission and/or due to limited availability of certain type of data e.g. a CAT score).

    o Incorrect data resulting from misunderstood questions in the electronic case report form (eCRF) as all documents being in English.

- Study sites may not be representative of the country, region or category and/or investigators may not be representative of the site.

- Selection bias (if not all eligible patients were approached for study participation) and not all eligible patients are equally likely to give consent.

- Observation bias (if non-comparable information is obtained for patients in different groups studied or with specific outcomes) and other predictable, potential confounders (differences between study groups in characteristics that are independent of the treatments being studied, but might have an impact on collected outcome data).

- A database design issue made the analysis of the the subscores for "activities" and "lung condition" not possible. As a result is was also not possible to analyze a total score for the CAT questionnaire.   Specification of data handling

Outlying values of spirometry parameters were not used in the analysis. Duplicities were removed from the analysis.

Summary of main characteristics and outcomes

Study population

Out of 1473 patient´s records, 1222 (83.0 %) were considered as valid patient´s records (i.e. patients who received at least one dose of Roflumilast and had at least one post treatment lung function or blood

oxygenation assessment). For countries, number of enrolled patients/number of valid patients´ records were as follow: Germany 615/421 (68.4 %), Slovakia 260/231 (88.8 %), Norway 86/65 (75.6 %), Greece 511/505 (98.8 %) and Bulgaria* 1/0 (0 %). Out of all enrolled patients only 115 (7.8 %) were fully completed (i.e. patients who had fulfilled all non-conditional fields in the database).

Analyses were prepared for the overall population and for 3 subgroups defined using COPD phenotypes. Phenotypes are dispersed in the valid patient´s sample as follows: emphysema phenotype by 61 (5.0 %), chronic bronchitis phenotype by 665 (54.4 %), and combination of both by 496 (40.6 %) patients.

* A total of 46 subjects were recruited from 5 centres in Bulgaria. Due to site attrition and despite repeated follow-up to ensure completion of data entry and eCRF sign-off, data for only one patient was signed at lock. However, the subejct did not meet criteria for inclusion to the valid patient record population. As a result, the patient data from Bulgaria was not valid for analysis.

Baseline characteristics

The valid patient´s sample includes 873 (71.4 %) males and 349 (28.6 %) females with median age 67 years. Out of the valid sample 133 (10.9 %) patients never smoked, 462 (37.8 %) are current smokers and 626 (51.2 %) are ex-smokers. The lung function impairment includes the most frequently severe 872 (71.4 %), then mild or moderate 222 (18.2 %) and very severe 128 (10.5 %) level of impairment. The median number of exacerbations 1 year prior the initiation of Roflumilast treatment was 2 exacerbations (5% - 95% percentile: 0 – 8). The most frequent reason for start treatment with Roflumilast was progression of COPD in 766 (62.7 %) patients, then high exacerbation rate in 690 (56.5 %), followed by inadequate response to existing / conventional treatment for COPD / exacerbation in 567 (46.4 %) patients.

More than half of subjects: 805 (65.9 %), was retiree/old age pensioner or on disability, the rest included working, unemployed persons and house-makers. The most frequent comorbidity was hypertension in 650 patients (53.2 %), others were less frequent (hypertension is followed by dyslipidemia in 259 (21.2 %), and coronary artery disease / (old) myocardial infarction in 215 (17.6 %) patients). The most frequent therapy used before initiation of study treatment was LAMA in 780 (63.8 %) patients, followed by LABA+ICS in 627 (51.3 %) and SABA in 593 (48.5 %) patients.

Summary of exacerbation frequency

Out of 1222 patients included in the valid sample, only 214 (17.5 %) had any exacerbation from treatment start to last visit; for these patients 316 exacerbations were recorded. Out of these 316 exacerbations, 263 (83.2 %) were treated with antibiotics, 222 (70.3 %) with systemic corticosteroids and 48 (15.2 %) with other medication; 90 (28.5 %) exacerbations needed hospitalization. Severity of exacerbations was not noted in the data. Out of 214 patients with any exacerbation 145 (11.9 %) patients had one exacerbation and 69 (5.6 %) patients had more than one exacerbation. The median number of exacerbations during one-year follow-up was 0 exacerbations (5% - 95% percentile: 0 – 2). For these groups of patients (0, 1, >1 exacerbation during the study) significant differences in following baseline characteristics were found: sex, race, smoking history, employment situation, change of employment due to COPD, age in categories, BMI in categories and number of cigarettes per day. For parameters related to COPD history, significant differences were found for lung function impairment, performance of oximetry and spirometry, history of chronic cough and sputum, airway infection during the last 12

months, pre bronchodilator FEV1 - Value [L], post bronchodilator FEV1 - Value [L], post bronchodilator FEV1 % pred [%], total number of COPD exacerbations prior Daxas treatment, COPD medication up to start of Daxas, greading of breathlessness, mMRC dyspnea index, phlegm, chest, breathlessness and energy in CAT questionnaire. Differences were found for many medications and comorbidities (Table 17b and 17d).

Details of results of exacerbations frequency are included in table series 16, 17, 18 and 19. Figure 1 and 2 show the time to first exacerbation overall and for phenotypes, respectively.

For table series 18 and 19, results have to be interpreted carefully as a very low number of patients had any exacerbation and therefore phenotype subgroups, as well as categorical parameters, could be unequally represented. Summary of significant odds ratios and hazard ratios are listed in following paragraphs.

For exacerbation occurrence following parameters were significant (e.g. patients have [XX.XX odds, below in the text, and its (95% CI)] times higher /lower odds to have at least one exacerbation during one year follow-up):

- Change of employment due to COPD
    - *For chronic bronchitis:* change of employment had 4.83 (2.82, 8.26) times higher odds than no change.
    - *For total set:* change of employment had 2.81 (1.86, 4.22) times higher odds than no change.

- Weight [kg] at baseline
    - *For combined subgroup:* Increment of baseline waist circumference value by one point was associated with lower odds (OR (total set) =0.98 (0.97, 1.00)) to have any exacerbation during one-year follow-up

- BMI categories
    - *For combined subgroup:* Patients Under weight or Normal (<25) had 2.57 (1.28, 5.42) times higher odds than obese (>30) patients to have any exacerbation during one-year follow-up

- Waist circumference [cm]
    - *For total set of patients and emphysema and chronic bronchitis subgroup:* Increment of baseline waist circumference value by one point was associated with higher odds (OR for total set =1.02 (1.01, 1.03), OR for emphysema = 1.06 (1.01, 1.14), OR for chronic bronchitis = 1.02 (1.01, 1.03)) to have any exacerbation during one-year follow-up

- Number of cigarettes per day
    - *For combined subgroup:* Increment of baseline number of cigarettes per day by one point was associated with lower odds (0.96 (0.91, 1.00)) to have any exacerbation during one-year follow-up

- o *For total set:* Increment of baseline <u>number of cigarettes per day</u> by one point was associated with lower odds (0.97 (0.95, 1.00)) to have any exacerbation during one-year follow-up

- <u>Comorbidities</u> (Patients with following comorbidities have [XX.XX (95% CI)] times higher/ lower odds to have at least one exacerbation during one year follow-up):

  - o Diabetes mellitus / Glucose intolerance

    - *For total set:* 1.64 (1.14, 2.36) times

    - *For emphysema subgroup:* 12.75 (1.91, 84.95) times

    - *For bronchitis subgroup:* 2.93 (1.82, 4.72) times

  - o Hypertension

    - *For total set:* 1.45 (1.07, 1.96) times

    - *For bronchitis subgroup:* 1.80 (1.18, 2.74) times

  - o Central obesity

    - *For bronchitis subgroup:* 1.94 (1.06, 3.53) times

  - o Dyslipidemia

    - *For total set:* 2.41 (1.74, 3.34) times

    - *For bronchitis subgroup:* 3.84 (2.51, 5.87) times

  - o Congestive heart failure

    - *For bronchitis subgroup:* 1.94 (1.06, 3.53) times

  - o Coronary artery disease / (old) Myocardial Infarction

    - *For total set*: 1.76 (1.23, 2.50) times

    - *For bronchitis subgroup:* 2.04 (1.25, 3.34) times

  - o Cerebrovascular disease, stroke or transient ischemia

    - *For total set*: 2.48 (1.22, 5.04) times

    - *For bronchitis subgroup:* 5.60 (2.11, 14.85) times

  - o Cor pulmonale

    - *For total set*: 1.72 (1.06, 2.81) times

    - *For bronchitis subgroup:* 2.15 (1.08, 4.26) times

  - o Cardiac arrhythmia

    - *For total set:* 3.93 (2.61, 5.92) times

    - *For bronchitis subgroup:* 5.23 (2.99, 9.15) times

    - *For combined subgroub:* 3.19 (1.67, 6.13) times

  - o Other cardiovascular disease

- *For total set*: 2.95 (1.61, 5.37) times

- *For bronchitis subgroup:* 4.43 (2.04, 9.58) times

  o Osteoporosis

    - *For total set*: 2.77 (1.73, 4.44) times

    - *For bronchitis subgroup:* 3.64 (2.00, 6.60) times

  o Other psychiatric disorder

    - *For total set*: 3.58 (1.42, 9.00) times

  o Recurrent pulmonary infections

    - *For total set*: 3.84 (1.83, 8.02) times

    - *For bronchitis subgroup:* 7.20 (2.68, 19.33) times

  o Myopathy

    - *For total set*: 5.74 (1.91, 17.26) times

    - *For bronchitis subgroup:* 7.15 (1.18, 43.31) times

    - *For combined subgroub:* 4.89 (1.20, 19.95) times

  o Anemia

    - *For total set*: 4.00 (1.84, 8.68) times

    - *For emphysema subgroup:* 10.40 (1.19, 90.56) times

    - *For bronchitis subgroup:* 6.42 (2.34, 17.61) times

  o Depression

    - *For total set*: 3.69 (2.32, 5.87) times

    - *For bronchitis subgroup:* 5.57 (3.00, 10.34) times

    - *For combined subgroub:* 2.55 (1.19, 5.49) times

  o Length of hypertension and displipidemia *for combined subgroup*: Increase of length of comorbidity by one point is associated with lower odds: 0.92 (0.85, 1.00) and 0.83 (0.70, 0.97) times respectively to have at least one exacerbation during one-year follow-up

  o Length of cardiac arrhythmia *for total set and bronchitis subgroup*: Increase of length of comorbidity by one point is associated with lower odds: 0.74 (0.60, 0.90) and 0.58 (0.38, 0.90) times respectively to have at least one exacerbation during one-year follow-up

  o Length of other cardiovascular disease *for total set*: Increase of length of comorbidity by one point is associated with lower odds: 0.69 (0.53, 0.90) times to have at least one exacerbation during one-year follow-up

- <u>mMRC dyspnoea index</u>

  o *For total set*: Increase of index by one point is associated with higher odds 1.39 (1.13, 1.73) times to have at least one exacerbation during one-year follow-up

- o *For bronchitis subgroup:* Increase of index by one point is associated with higher odds 1.59 (1.20, 2.13) times to have at least one exacerbation during one-year follow-up

- CAT questionnaire (Increment/Decreament in baseline CAT categories by one point was associated with [XX.XX (95% CI)] times higher/lower odds to have at least one exacerbation during one year follow-up):

  - o Cough

    - *For bronchitis subgroup*: 1.25 (1.01, 1.54) times

  - o Phlegm

    - *For total set*: 1.21 (1.05, 1.39) times

    - *For emphysema subgroup:* 6.21 (1.70, 55.75) times

    - *For bronchitis subgroup:* 1.44 (1.17, 1.78) times

  - o Chest

    - *For total set*: 1.23 (1.09, 1.40) times

    - *For emphysema subgroup:* 2.84 (1.22, 9.06) times

    - *For bronchitis subgroup:* 1.51 (1.26, 1.83) times

  - o Breathless

    - *For total set*: 1.46 (1.24, 1.74) times

    - *For bronchitis subgroup:* 1.47 (1.17, 1.85) times

    - *For combined subgroup:* 1.48 (1.12, 1.99) times

  - o Sleep

    - *For emphysema subgroup:* 3.07 (1.24, 11.84) times

    - *For bronchitis subgroup:* 1.32 (1.12, 1.57) times

  - o Energy

    - *For total set*: 1.22 (1.07, 1.39) times

    - *For emphysema subgroup:* 3.27 (1.20, 12.32) times

    - *For bronchitis subgroup:* 1.41 (1.16, 1.73) times

- Exacerbation at time of first prescribing roflumilast

  - o *For combined subgroup:* Exacerbation at time of the first prescribing roflumilast is associated with lower odds 0.52 (0.31, 0.88) to have any exacerbation during one-year follow-up.

- Reason for initiation of roflumilast

  - o *For total set:* High exacerbation rate is associated with higher odds 1.39 (1.06, 1.82) to have any exacerbation during one-year follow-up than for progression of COPD.

- Lung function impairment

  o *For total set:* Very severe impairment is associated with higher odds 2.31 (1.29, 4.17) to have any exacerbation during one-year follow-up than for mild/moderate impairment

  o *For chronic bronchitis:* Very severe impairment is associated with higher odds 2.51 (1.02, 6.11) to have any exacerbation during one-year follow-up than for mild/moderate impairment

- Oxymetry test

  o *For total set:* In case of no examination by oxymetry lower odds 0.51 (0.33, 0.77) are revealed to have any exacerbation during one-year follow-up than for examined patients.

  o *For chronic bronchitis:* In case of no examination by oxymetry lower odds 0.44 (0.25, 0.75) are revealed to have any exacerbation during one-year follow-up than for examined patients.

- History of chronic cough and sputum

  o *For total set:* No (or not known) history of chronic cough and sputum is associated with lower odds 0.29 (0.09, 0.72) to have any exacerbation during one-year follow-up.

- Airway infection during the last 12 months

  o *For total set:* No (or not known) infection during the last 12 months is associated with lower odds 0.59 (0.33, 0.99) to have any exacerbation during one-year follow-up.

- Age at diagnosis

  o *For total set:* Increment of age at diagnosis by one point is associated with lower odds (OR=0.98 (0.96, 0.99)) to have any exacerbation during one-year follow-up

  o *For chronic bronchitis subgroup:* Increment of age at diagnosis by one point is associated with lower odds (OR=0.98 (0.96, 1.00)) to have any exacerbation during one-year follow-up

  o *For chronic combined subgroup:* Increment of age at diagnosis by one point is associated with lower odds (OR=0.97 (0.95, 1.00)) to have any exacerbation during one-year follow-up

- Pre bronchodilator FEV1 - Value [L]

  o *For total set:* Increment of Pre bronchodilator FEV1 - Value [L] by one point is associated with lower odds (OR=0.66 (0.46, 0.92)) to have any exacerbation during one-year follow-up

  o *For chronic bronchitis subgroup:* Increment of Pre bronchodilator FEV1 - Value [L] by one point is associated with lower odds (OR=0.59 (0.36, 0.92)) to have any exacerbation during one-year follow-up

- Pre bronchodilator FEV1 - % pred [%]

- o *For total set:* Increment of <u>Pre bronchodilator FEV1 - % pred [%]</u> by one point is associated with lower odds (OR=0.98 (0.97, 0.99)) to have any exacerbation during one-year follow-up

- o *For chronic bronchitis subgroup:* Increment of <u>Pre bronchodilator FEV1 - % pred [%]</u> by one point is associated with lower odds (OR=0.98 (0.96, 0.99)) to have any exacerbation during one-year follow-up

- <u>Post bronchodilator FEV1 - Value [L]</u>

  - o *For total set:* Increment of <u>Post bronchodilator FEV1 - Value [L]</u> by one point is associated with lower odds (OR=0.61 (0.43, 0.85)) to have any exacerbation during one-year follow-up

  - o *For chronic bronchitis subgroup:* Increment of <u>Post bronchodilator FEV1 - Value [L]</u> by one point is associated with lower odds (OR=0.41 (0.24, 0.66)) to have any exacerbation during one-year follow-up

- <u>Post bronchodilator FEV1 - % pred [%]</u>

  - o *For total set:* Increment of <u>Post bronchodilator FEV1 - % pred [%]</u> by one point is associated with lower odds (OR=0.97 (0.96, 0.98)) to have any exacerbation during one-year follow-up

  - o *For chronic bronchitis subgroup:* Increment of <u>Post bronchodilator FEV1 - % pred [%]</u> by one point is associated with lower odds (OR=0.96 (0.95, 0.98)) to have any exacerbation during one-year follow-up

  - o *For combined subgroup:* Increment of <u>Post bronchodilator FEV1 - % pred [%]</u> by one point is associated with lower odds (OR=0.98 (0.96, 1.00)) to have any exacerbation during one-year follow-up

- <u>Total number of COPD exacerbations prior Daxas treatment</u>

  - o *For total set:* Increment of <u>number of COPD exacerbations</u> by one point is associated with higher odds (OR=1.07 (1.03, 1.12)) to have any exacerbation during one-year follow-up

  - o *For chronic bronchitis subgroup:* Increment of <u>number of COPD exacerbations</u> by one point is associated with higher odds (OR=1.09 (1.03, 1.16)) to have any exacerbation during one-year follow-up

- <u>Therapy</u> (Patients with following therapy have [XX.XX (95% CI)] times high/less odd to have at least one exacerbation during one year follow-up):

  - o <u>SAMA</u>

    - ▪ *For chronic bronchitis subgroup:* 1.76 (1.08, 2.87) times

  - o <u>LAMA</u>

    - ▪ *For total set:* 1.81 (1.27, 2.58) times

    - ▪ *For chronic bronchitis subgroup:* 1.64 (1.04, 2.60) times

- *For combined subgroup:* 2.46 (1.31, 4.60) times
    - SABA
        - *For total set:* 1.71 (1.26, 2.34) times
        - *For chronic bronchitis subgroup:* 1.82 (1.20, 2.76) times
    - LABA
        - *For chronic bronchitis subgroup:* 0.65 (0.42, 1.00) times
    - SAMA+LABA
        - *For chronic bronchitis subgroup:* 1.93 (1.11, 3.36), times
    - LABA+ICS
        - *For total set of patients*: 2.05 (1.49, 2.82) times
        - *For chronic bronchitis subgroup:* 2.39 (1.56, 3.66) times
        - *For combined subgroup:* 2.11 (1.24, 3.59) times
    - Long term oxygen therapy
        - *For total set of patients*: 1.53 (1.03, 2.29) times
        - *For combined subgroup:* 1.98 (1.13, 3.47) times

Following significant factors influencing the time to first exacerbation were find out (e.g. patients have XX.XX (95% CI) times high /less risk to have at least one exacerbation during one year follow-up):

- Change of employment due to COPD
    - *For total set of patients*: Patients changing employment due to COPD have 2.40 (1.71, 3.35) times high risk to have at least one exacerbation during one-year follow-up
    - *For chronic bronchitis subgroup:* Patients changing employment due to COPD have 3.62 (2.40, 5.47) times high risk to have at least one exacerbation during one-year follow-up

- Weight at baseline
    - *For combined subgroup:* Increment of weight by one point is associated with lower risk 0.98 (0.97, 1.00) to have at least one exacerbation during one-year follow-up

- BMI at baseline
    - *For combined subgroup:* Increment of BMI by one point is associated with lower risk 0.95 (0.91, 0.99) to have at least one exacerbation during one-year follow-up

- BMI categories
    - *For combined subgroup:* Patients Under weight or Normal (<25) have 2.64 (1.40, 4.97) times higher risk and Overweight (25-30) have 1.95 (1.03, 3.67) times higher risk than obese (>30) patients to have any exacerbation during one-year follow-up.

- Waist circumference [cm]

o *For total set of patients and chronic bronchitis subgroup:* Increment of baseline waist circumference value by one point was associated with higher risk (HR for both =1.02 (1.01, 1.03)) to have any exacerbation during one-year follow-up

- Number of cigarettes per day
    o *For total set:* Increment of baseline <u>number of cigarettes per day</u> by one point was associated with lower risk (0.97 (0.95, 0.99) to have any exacerbation during one-year follow-up
    o *For bronchitis subgroup:* Increment of baseline <u>number of cigarettes per day</u> by one point was associated with lower risk (0.97 (0.94, 1.00)) to have any exacerbation during one-year follow-up

- Comorbidities (Patients with following comorbidities have [XX.XX (95% CI)] times high/less risk to have at least one exacerbation during one year follow-up):
    o Clinically significant bronchiectasis
        ▪ *For total set of patients:* 1.75 (1.04, 2.97) times
        ▪ *For chronic bronchitis subgroup:* 2.54 (1.18, 5.46) times
    o Rheumatoid arthritis
        ▪ *For total set of patients:* 2.28 (1.12, 4.63) times
        ▪ *For combined subgroup:* 2.78 (1.13, 6.88) times
    o Diabetes mellitus / Glucose intolerance:
        ▪ *For total set of patients:* 1.53 (1.10, 2.13) times
        ▪ *For emphysema subgroup:* 7.95 (1.77, 35.62) times
        ▪ *For chronic bronchitis subgroup:* 2.50 (1.66, 3.77) times
    o Hypertension
        ▪ *For total set of patients:* 1.37 (1.03, 1.82) times
        ▪ *For chronic bronchitis subgroup:* 1.78 (1.19, 2.65) times
    o Central obesity
        ▪ *For chronic bronchitis subgroup:* 1.81 (1.08, 3.04) times
    o Dyslipidemia
        ▪ *For total set of patients:* 2.13 (1.59, 2.84) times
        ▪ *For chronic bronchitis subgroup:* 3.29 (2.27, 4.77) times
    o Other cancer
        ▪ *For chronic bronchitis subgroup:* 3.19 (1.17, 8.66) times
    o Congestive heart failure

- ▪ *For chronic bronchitis subgroup:* 2.43 (1.41, 4.18) times
- o Coronary artery disease / (old) Myocardial Infarction
    - ▪ *For total set of patients:* 1.63 (1.18, 2.24) times
    - ▪ *For chronic bronchitis subgroup:* 1.91 (1.24, 2.95) times
- o Cerebrovascular disease, stroke or transient ischemia
    - ▪ *For total set of patients*: 2.16 (1.21, 3.88) times
    - ▪ *For chronic bronchitis subgroup:* 4.05 (2.05, 8.01) times
- o Cor pulmonale
    - ▪ *For total set of patients:* 1.66 (1.08, 2.55) times
    - ▪ *For chronic bronchitis subgroup:* 1.89 (1.05, 3.38) times
- o Cardiac arrhythmia
    - ▪ *For total set of patients:* 3.32 (2.39, 4.61) times
    - ▪ *For chronic bronchitis subgroup:* 4.28 (2.79, 6.58) times
    - ▪ *For combined subgroup:* 2.75 (1.62, 4.69) times
- o Other cardiovascular disease
    - ▪ *For total set of patients:* 2.69 (1.65, 4.36) times
    - ▪ *For chronic bronchitis subgroup:* 3.72 (2.08, 6.63) times
- o Osteoporosis
    - ▪ *For total set of patients:* 2.57 (1.74, 3.79) times
    - ▪ *For chronic bronchitis subgroup:* 3.13 (1.95, 5.04) times
- o Other psychiatric disorder
    - ▪ *For total set of patients:* 2.66 (1.31, 5.39) times
- o Recurrent pulmonary infections
    - ▪ *For total set of patients:* 3.30 (1.88, 5.78) times
    - ▪ *For chronic bronchitis subgroup:* 4.98 (2.60, 9.57) times
- o Myopathy
    - ▪ *For total set of patients:* 4.39 (2.07, 9.34) times
    - ▪ *For chronic bronchitis subgroup:* 5.69 (1.80, 17.95) times
    - ▪ *For combined subgroup:* 3.68 (1.35, 10.05) times
- o Anemia
    - ▪ *For total set of patients:* 3.27 (1.82, 5.86) times
    - ▪ *For emphysema subgroup:* 7.18 (1.38, 37.32) times

- - - *For chronic bronchitis subgroup:* 4.31 (2.18, 8.53) times
  - o Depression
    - - *For total set of patients:* 3.17 (2.19, 4.58) times
    - - *For chronic bronchitis subgroup:* 4.04 (2.55, 6.40) times
    - - *For combined subgroup:* 2.59 (1.37, 4.90) times
  - o Length of dyslipidemia
    - - *For combined subgroup:* 0.83 (0.71, 0.97) times
  - o Length of cardiac arrhythmia
    - - *For total set of patients:* 0.81 (0.70, 0.93) times
    - - *For chronic bronchitis subgroup:* 0.73 (0.58, 0.91) times
  - o Length of other cardiovascular disease
    - - *For total set of patients:* 0.76 (0.61, 0.94) times
    - - *For chronic bronchitis subgroup:* 0.82 (0.69, 0.98) times

- mMRC dyspnea index
  - o *For total set of patients:* Increment of mMRC index by one point was associated with higher risk (HR=1.34 (1.11, 1.62)) to have any exacerbation during one-year follow-up
  - o *For chronic bronchitis subgroup:* Increment of mMRC index by one point was associated with higher risk (HR=1.51 (1.18, 1.94)) to have any exacerbation during one-year follow-up

- CAT questionnaire (Increment in baseline CAT categories by one point was associated with [XX.XX (95% CI)] times higher/lower risk to have at least one exacerbation during one year follow-up):
  - o Cough
    - - *For emphysema subgroup*:   9.80 (1.51, 63.64) times
    - - *For chronic bronchitis subgroup*: 1.24 (1.02, 1.51) times
  - o Phlegm
    - - *For total set of patients:* 1.20 (1.06, 1.37) times
    - - *For emphysema subgroup:* 4.78 (1.36, 16.84) times
    - - *For chronic bronchitis subgroup:* 1.44 (1.19, 1.75) times
  - o Chest
    - - *For total set of patients:* 1.23 (1.10, 1.38) times
    - - *For emphysema subgroup:* 2.59 (1.14, 5.88) times
    - - *For chronic bronchitis subgroup:* 1.49 (1.26, 1.76) times

- o Breathlessness

    - *For total set of patients:* 1.46 (1.25, 1.71) times

    - *For chronic bronchitis subgroup:* 1.46 (1.19, 1.79) times

    - *For combined subgroup:* 1.49 (1.15, 1.93) times

  - o Sleep

    - *For emphysema subgroup:* 3.07 (1.21, 7.83) times

    - *For chronic bronchitis subgroup:* 1.30 (1.11, 1.52) times

  - o Energy

    - *For total set of patients:* 1.18 (1.05, 1.34) times

    - *For emphysema subgroup:* 3.02 (1.22, 7.49) times

    - *For chronic bronchitis subgroup:* 1.36 (1.14, 1.63) times

- Exacerbation at time of first prescribing Roflumilast

  - o *For combined subgroup:* Absence of exacerbation at time of first exacerbation is associated with lower risk to have any exacerbation during one-year follow-up

- Reason for initiation of Roflumilast

  - o *For total set of patients:* Patients with high exacerbation rate have 1.38 (1.09, 1.76) higher risk to have any exacerbation during one-year follow-up than patients with progression of COPD

  - o *For chronic bronchitis subgroup:* Patients with high exacerbation rate have 1.41 (1.03, 1.92) higher risk to have any exacerbation during one-year follow-up than patients with progression of COPD

- Lung function impairment

  - o *For total set of patients:* Patients with very severe lung function impairment have 2.10 (1.28, 3.44) higher risk to have any exacerbation during one-year follow-up than patients with mild/moderate lung function impairment

  - o *For chronic bronchitis subgroup:* Patients with very severe lung function impairment have 2.12 (1.01, 4.45) higher risk to have any exacerbation during one-year follow-up than patients with mild/moderate lung function impairment

- Oxymetry

  - o *For total set of patients:* Patients without performance of oximetry have 0.48 (0.33, 0.71) lower risk to have any exacerbation during one-year follow-up than patients with performed oxymetry

  - o *For chronic bronchitis subgroup:* Patients without performance of oximetry have 0.39 (0.24, 0.65) lower risk to have any exacerbation during one-year follow-up than patients with performed oxymetry

- History of chronic cough and sputum

- o *For total set of patients:* Patients without history of chronic cough and sputum have 0.32 (0.13, 0.79) lower risk to have any exacerbation during one-year follow-up than patients with history of chronic cough and sputum

- Age at diagnosis

    - o *For total set of patients:* Increment of age at diagnosis by one point was associated with lower risk (HR=0.98 (0.96, 0.99)) to have any exacerbation during one-year follow-up

    - o *For chronic bronchitis subgroup:* Increment of age at diagnosis by one point was associated with lower risk (HR=0.98 (0.96, 1.00)) to have any exacerbation during one-year follow-up

    - o *For combined subgroup:* Increment of age at diagnosis by one point was associated with lower risk (HR=0.97 (0.93, 0.99)) to have any exacerbation during one-year follow-up

- Pre bronchodilator FEV1 - Value [L]

    - o *For total set of patients*: Increment of Pre bronchodilator FEV1 - Value [L] by one point was associated with lower risk (HR=0.70 (0.51, 0.97)) to have any exacerbation during one-year follow-up

- Pre bronchodilator FEV1 - % pred [%]

    - o *For total set of patients:* Increment of Pre bronchodilator FEV1 - % pred [%] by one point was associated with lower risk (HR=0.98 (0.97, 1.00)) to have any exacerbation during one-year follow-up

    - o *For chronic bronchitis subgroup*: Increment of Pre bronchodilator FEV1 - % pred [%] by one point was associated with lower risk (HR=0.98 (0.97, 1.00)) to have any exacerbation during one-year follow-up

- Post bronchodilator FEV1 - Value [L]

    - o *For total set of patients*: Increment of Pre Post bronchodilator FEV1 - Value [L] by one point was associated with lower risk (HR=0.65 (0.48, 0.89)) to have any exacerbation during one-year follow-up

    - o *For chronic bronchitis subgroup:* Increment of Post bronchodilator FEV1 - Value [L] by one point was associated with lower risk (HR=0.47 (0.30, 0.75)) to have any exacerbation during one-year follow-up

- Post bronchodilator FEV1 - % pred [%]

    - o *For total set of patients:* Increment of Post bronchodilator FEV1 - % pred [%] by one point was associated with lower risk (HR=0.97 (0.96, 0.99)) to have any exacerbation during one-year follow-up

    - o *For chronic bronchitis subgroup*: Increment of Post bronchodilator FEV1 - % pred [%] by one point was associated with lower risk (HR=0.97 (0.95, 0.99)) to have any exacerbation during one-year follow-up

o *For combined subgroup:* Increment of Post bronchodilator FEV1 - % pred [%] by one point was associated with lower risk (HR=0.98 (0.96, 1.00)) to have any exacerbation during one-year follow-up

- Total number of COPD exacerbations prior Daxas treatment

  o *For total set of patients:* Increment of number of COPD exacerbations by one point was associated with higher risk (HR=1.06 (1.03, 1.10)) to have any exacerbation during one-year follow-up

  o *For chronic bronchitis subgroup*: Increment of number of COPD exacerbations by one point was associated with higher risk (HR=1.08 (1.03, 1.12)) to have any exacerbation during one-year follow-up

- Therapy (Patients with following therapy have [XX.XX (95% CI)] times high/less risk to have at any exacerbation during one year follow-up):

  o SAMA

    ▪ *For chronic bronchitis subgroup:* 1.65 (1.07, 2.54) times

  o LAMA

    ▪ *For total set:* 1.63 (1.17, 2.26) times

    ▪ *For combined subgroup:* 2.16 (1.20, 3.91) times

  o SABA

    ▪ *For total set:* 1.62 (1.22, 2.16) times

    ▪ *For chronic bronchitis subgroup:* 1.73 (1.18, 2.54) times

  o LABA

    ▪ *For chronic bronchitis subgroup:* 0.64 (0.43, 0.95) times

  o SAMA+LABA

    ▪ *For chronic bronchitis subgroup:* 1.77 (1.09, 2.87) times

  o LABA+ICS

    ▪ *For total set of patients*: 1.86 (1.38, 2.50) times

    ▪ *For chronic bronchitis subgroup:* 2.22 (1.49, 3.31) times

    ▪ *For combined subgroup:* 1.87 (1.14, 3.06) times

  o Long term oxygen therapy

    ▪ *For total set of patients*: 1.59 (1.11, 2.26) times

    ▪ *For combined subgroup:* 1.96 (1.20, 3.19) times

  o Leukotriene antagonist

- *For Emphysema subgroup*: 5.45 (1.21, 24.54) times

Summary of additional endpoints

Table series 12, 13, 14 and 15 include the results of the analysis of longitudinal measures. Spirometry and oximetry parameters, mMRC scale, CAT questionnaire, weight and BMI were adjusted for confounding factors and covariates. As time and phenotype were primary variables of interest and were used as "fixed" variables in GEE models, confounding factors and covariates were used individually for testing its significance. More complex combinations of variables were not modeled because of the increasing complexity of models along with the insufficient sample size can cause biased results (i.e. over-fitting).

The following list summarizes the statistically significant covariates for the examined parameters mentioned in previous paragraph:

- pre bronchodilator FEV1 [L]
  - Time
  - Smoking history
  - Age at baseline
  - Out of comorbidities: asthma, clinically significant bronchiectasis , cerebrovascular disease, stroke or transient ischemic attack, depression, length of congestive heart failure, other cardiovascular disease, anemia, rheumatoid arthritis
  - Out of therapy: leukotriene antagonist, LAMA, LABA
  - Grade degree of breathlessness related to activities
  - mMRC dyspnoea index
  - Out of CAT questionnaire: chest
- post bronchodilator FEV1 [L]
  - Time
  - Phenotype
  - Waist circumference
  - Out of comorbidities: psoriasis, clinically significant bronchiectasis, depression, length of other cardiovascular disease, of other psychiatric disorder
  - Grade degree of breathlessness related to activities
- post bronchodilator FVC
  - Time
  - Out of comorbidities: peripheral vascular disease
  - Lung function impairment

- o   Out of therapy: SAMA,

- SpO2

  - o   Number of cigarettes per day

    - o   Out of comorbidities: diabetes mellitus / glucose intolerance, hypertension, dyslipidemia, lung cancer, clinically significant bronchiectasis, cor pulmonale, osteoporosis, myopathy, chronic kidney disease and/or chronic renal failure, depression

  - o   Lung function impairment

  - o   Airway infection during the last 12 months

  - o   COPD exacerbation

- mMRC

  - o   Time

  - o   Phenotype

  - o   Out of comorbidities: hypertension, dyslipidemia, clinically significant bronchiectasis, length of central obesity, coronary artery disease / (old) myocardial infarction, depression

  - o   COPD exacerbation

  - o   Out of therapy: long term oxygen therapy, leukotriene antagonist, lenght of SAMA+LABA

  - o   Out of CAT questionnaire: all subscores

- CAT questionnaire: cough

  - o   Time

  - o   Waist circumference

  - o   Number of cigarettes per day

  - o   Out of comorbidities: asthma, coronary artery disease / (old) myocardial infarction, other cardiovascular disease, depression, length of asthma, other psychiatric disorder

  - o   Lung function impairment

  - o   History of chronic cough and sputum

  - o   Airway infection during the last 12 months

  - o   COPD exacerbations

  - o   Out of therapy: LAMA

- CAT questionnaire: phlegm

  - o   Time

  - o   Waist circumference

- o Out of comorbidities: clinically significant bronchiectasis, other cardiovascular disease, osteoporosis, myopathy, anemia, length of asthma, clinically significant bronchiectasis, other psychiatric disorder, depression

- o Lung function impairment

- o History of chronic cough and sputum

- o Airway infection during the last 12 months

- o COPD exacerbation

- o Out of therapy: SABA, Theophylline or derivates

- CAT questionnaire: chest

  - o Time

  - o Sex

  - o Waist circumference

  - o Number of cigarettes per day

    - o Out of comorbidities: asthma, clinically significant bronchiectasis, osteoporosis, myopathy, anemia, depression, length other psychiatric disorder

  - o History of chronic cough and sputum

  - o Airway infection during the last 12 months

  - o COPD exacerbation

  - o Out of therapy: Theophylline or derivates, long term oxygen therapy

- CAT questionnaire: breathlessness

  - o Race

  - o Time

  - o Smoking history

  - o Waist circumference

  - o Number of cigarettes per day

  - o Out of comorbidities: myopathy, length of asthma

  - o History of chronic cough and sputum

  - o Airway infection during the last 12 months

  - o Post bronchodilator FEV1 - Value [L]

  - o Post bronchodilator FVC - Value [L]

  - o Out of therapy: SABA, SABA+SAMA, Theophylline or derivates

- CAT questionnaire: Sleep

- o Time

- o Waist circumference

- o Out of comorbidities: coronary artery disease / (old) myocardial infarction, clinically significant bronchiectasis, other cardiovascular disease, myopathy, length of cardiac arrhythmia, other psychiatric disorder

- o Post bronchodilator FEV1 - Value [L]

- o COPD exacerbations

- o Out of therapy: SABA+SAMA, long term oxygen therapy

- CAT questionnaire: energy

  - o Time

  - o Waist circumference

  - o Number of cigarettes per day

  - o Out of comorbidities: congestive heart failure, other cardiovascular disease, depression, rheumatoid arthritis, length of asthma, cardiac arrhythmia, recurrent pulmonary infections

  - o History of chronic cough and sputum

  - o Post bronchodilator FEV1 - Value [L]

  - o COPD exacerbations

  - o Out of therapy: SAMA, SABA+SAMA, long term oxygen therapy

- Weight

  - o Time

  - o Phenotype

  - o Sex

  - o Height

  - o BMI

  - o Waist circumference

  - o Out of comorbidities: diabetes mellitus / glucose intolerance, central obesity, dyslipidemia, other cardiovascular disease, cardiac arrhythmia, depression, length of cardiac arrhythmia, of other cardiovascular disease

  - o History of chronic cough or sputum

  - o COPD exacerbation

  - o Out of therapy: LABA, length of LABA+ICS, of Theophylline or derivates

  - o Out of CAT questionnaire: cough, phlegm

- BMI

- o   Time

- o   Phenotype

- o   Sex

- o   Weight

- o   Height

- o   Waist circumference

- o   Number of cigarettes per day

- o   Out of comorbidities: diabetes mellitus / glucose intolerance, central obesity, dyslipidemia, cardiac arrhythmia, other cardiovascular disease, myopathy, chronic kidney disease and/or chronic renal failure, depression, length of cardiac arrhythmia, of other cardiovascular disease

- o   History of chronic cough or sputum

- o   COPD exacerbation

- o   Out of therapy: LABA, length of LABA+ICS, of Theophylline or derivates

- o   Out of CAT questionnaire: cough, phlegm

Safety (Adverse Events)

During the conduct of the non - interventional   study centers reported 207 cases of adverse events of which 74 cases were assessed as serious cases. The cases occurred in 134 / (52 serious)   male patients and 62 / (13 serious)   female patients and 11/(9 serious) with gender unreported . The majority of cases were reported in the age group over 65 years with almost 70% of the cases.

From these cases in total 354 treatment emergent adverse events were reported with a range of 1 – 10 adverse events per patient. The 74 serious cases reported in total 102 adverse events of serious nature.

291 adverse events were assessed with a possible relationship to the treatment while 62 were assessed not related.

By SOC classes the distribution of AEs is as shown in the below table, where the majority of nearly one third of the reported cases belong to the class of gastrointestinal disorders. Here terms like diarrhea, nausea and upper abdominal pain were the most often reported terms.

AE_SOC	
Events per SOC - Class	Count of Event SOC Name
Cardiac disorders	20
Ear and labyrinth disorders	3

AE_SOC	
Events per SOC - Class	**Count of Event SOC Name**
Gastrointestinal disorders	108
General disorders and administration site conditions	38
Infections and infestations	13
Injury, poisoning and procedural complications	15
Investigations	15
Metabolism and nutrition disorders	12
Musculoskeletal and connective tissue disorders	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8
Nervous system disorders	18
Psychiatric disorders	18
Renal and urinary disorders	1
Respiratory, thoracic and mediastinal disorders	65
Skin and subcutaneous tissue disorders	8
Surgical and medical procedures	2
Vascular disorders	4

As a summary the reported AEs present the known profile of adverse reactions described in the SmPC for Roflumilast.

Results

Two hundred and fourteen of the 1222 patients enrolled in the study (17.5 %) experienced one or more exacerbation(s) during the one-year follow-up. Of these patients 145 (11.9 %) patients had one exacerbation and 69 (5.6 %) patients had more than one exacerbation. The median number of exacerbations 1 year prior the initiation of roflumilast treatment was 2 exacerbations (5% - 95% percentile: 0 – 8), after 1 year follow-up 0 exacerbations (5% - 95% percentile: 0 – 2). There was no significant differences in the exacerbation frequency between COPD phenotypes (emphysema, chronic bronchitis, and combined phenotype). Median time to first exacerbation was not identified. Mean time to first exacerbation was 476.54 days.

Conclusion:

These results suggest that the use of roflumilast (Daxas®) in standard clinical practice may reduce the frequency of exacerbations in patients with COPD.