Clinical Study Report Synopsis

Drug Substance	Roflumilast
Study Code	RO-2455-407-RD
Edition Number	1.0
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The PROFILE Study, Patient Registry of ROFlumilast In Real LifE

Study dates:	First subject enrolled: 11 February 2013 Last subject last visit: 16 February 2016
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca AB

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The PROFILE study was conducted in 5 European countries (Bulgaria, Germany, Greece, Norway and Slovakia).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			**Outcome Variable**
Priority	**Type**	**Description**	**Description**
Primary	*Efficacy*	Frequency of exacerbations	Absolute and relative count of exacerbations, total and by subgroups (COPD phenotype, smoking status, lung functions, initial CAT score, initial mMRC score, comorbidities, change of employment)
Primary	*Efficacy*	Time between exacerbations	Time from treatment start to exacerbation occurrence
Primary	*Efficacy*	Management of exacerbations	Co-medication, hospitalization
Secondary	*Efficacy*	Lung function	Lung function impairment, airway infections, history of chronic cough and sputum, lung function measurements (FEV1, FVC, SpO2)
Secondary	*Efficacy*	Weight measurements	Weight, BMI, Waist circumference
Secondary	*Efficacy*	Quality of life	CAT questionnaire
Secondary	*Efficacy*	COPD symptoms	mMRC index
Secondary	*Efficacy*	Development of new comorbidities	Comorbidity occurrence
Other	*Exploratory*	Exploration of primary endpoints	Confounding factors analyses
Other	*Exploratory*	Exploration of secondary endpoints	Confounding factors analyses
Other	*Safety*	Frequency of SAEs and SADRs	Counts of SAEs and SADRs
Other	*Safety*	Rescue therapy	Dose increase/dose decrease/drug discontinuation/addition of drug during the study
Other	*Efficacy*	Treatment compliance	Reason for treatment initiation and discontinuation, percentage of Daxas treatment compliance

Study design

The PROFILE study was an observational, non-interventional, prospective cohort study as defined by the directive 2001/20/EC and will follow the guidelines for GPP.

The patients have been followed for 12 months after enrolment.

Target subject population and sample size

All available patients using Daxas were enrolled in the registry. This study was not designated to conduct any formal statistical inferences. The possible number of patients in each country was estimated on feedback from sites, and adjusted with projection on budget and timeline. This study was designed to capture real life data and to demonstrate the performance of roflumilast (Daxas®) in standard clinical practice.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Roflumilast (Daxas®) is a novel oral therapy indicated for maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment.

Duration of treatment

One year

Statistical methods

Standard descriptive statistics were used in the analysis. For the comparison of subgroups and for changes from baseline statistical tests were applied (Kruskal Wallis test; Mann-Whitney U test, Fisher exact). The change of variables in time was modelled and tested using GEE (generalized estimating equation) for the analysis of longitudinal measures. Effects of occurrence of exacerbations were evaluated using logistic regression and time-to-event analysis.

Subject population

Out of 1473 patient ś records, 1222 (83.0 %) were considered as valid patient ś 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 performed in the overall population and 3 subgroups defined using COPD phenotypes. Phenotypes are dispersed in the valid patient ś sample as follows: emphysema by 61 (5.0 %), chronic bronchitis by 665 (54.4 %), and combination of both by 496 (40.6 %) patients.

Out of valid patient sample, 1046 (85.6 %) patients were completed as planned and 1008 (82.5%) patients continue with Daxas treatment after study end.

The valid patient ś 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.

More than half of subjects: 805 (65.9 %), were retirees/old age pensioners 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 dyslipidaemia 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.

* 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 subject 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.

Summary of efficacy results

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 led to hospitalization. Severity of exacerbations was not noted in the data. The median number of exacerbations during one-year follow-up was 0 exacerbations (5% - 95% percentile: 0 – 2) irrespective ofphenotype. There was no significant differences in the exacerbation frequency between COPD phenotypes (emphysema, chronic bronchitis, and combined phenotype). The median number of exacerbations 1 year prior to the initiation of Roflumilast treatment was 2 exacerbations (5% - 95% percentile: 0 – 8), for emphysema phenotype 1 (0 – 4), for chronic bronchitis 2 (0 – 8) and for combined 2 (0 – 8). The decrease of exacerbations with Daxas treatment is therefore considerable. 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.

Out of 214 patients with any exacerbation 145 (11.9 %) patients had one exacerbation and 69 (5.6 %) patients had more than one exacerbation during one year follow-up. During one year prior to study start, these counts were higher: 199 (16.3 %) patients with 1 exacerbation and 757 (61.9 %) with more than one exacerbation. For these groups of patients (0, 1, >1 exacerbation during the study) significant differences in following baseline characteristics were found:

- sex (more than one exacerbation were more often in males),
- smoking history (more than one exacerbation were more often for current smokers),
- employment situation (ratio of working persons increase with number of exacerbations),
- change of employment due to COPD (ratio of patients which have to change employment increase with number of exacerbations),
- age in categories (significant result, but trend is not visible),
- BMI in categories (more than one exacerbation were more often for normal BMI),
- number of cigarettes per day (patients with more than one exacerbation use less cigarettes)

For parameters related to COPD history, significant differences were found for:

- lung function impairment (more than one exacerbation were more often in very severe),
- performance of oximetry and spirometry (these two assessments were performed more often for patient with more exacerbations),
- history of chronic cough and sputum and airway infection during the last 12 months (these two assessments were present more often for patient with more exacerbations),
- pre bronchodilator FEV1 - Value [L], post bronchodilator FEV1 - Value [L], post bronchodilator FEV1 % pred [%] (value is lower for patients with more than one exacerbations),
- total number of COPD exacerbations prior Daxas treatment (value is higher for patients with more than one exacerbations),
- COPD medication up to start of Daxas (higher for patients with exacerbations),
- greading of breathlessness (higher for patients with exacerbations),
- phlegm, chest, breathlessness and energy in CAT questionnaire (higher for patients with exacerbations).

Differences were found for many medications and comorbidities (comorbidities with $p<0.0001$: Dyslipidemia, Coronary artery disease / (old) Myocardial Infarction, Cor pulmonale, Cardiac arrhythmia, Other cardiovascular disease Osteoporosis, Recurrent pulmonary infections, Depression, medication with $p<0.0001$: LAMA, SABA, LABA+ICS).

Beyond descriptive analyses of exacerbations, analyses of odds and risk were performed. The most significant results were found in the chronic bronchitis subgroup. Median time to first exacerbation was not identified for all patient nor for all phenotypes since more than one half of patient did not experience any exacerbation during one-year follow-up. Mean time to first exacerbation is 476.54 days for all patients, 167.94 days for emphysema subgroup, 474.15 days for chronic bronchitis subgroup and 332.84 days for combined subgroup.

Analyses of odds and risk ratios are not presented in details because they should 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 study report.

Summary of safety results

During the conduct of the study centres 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, a total of 354 treatment emergent adverse events were reported with a range of 1 – 10 adverse events per patient. The 74 serious cases reported in total of 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 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 diarrhoea, nausea and upper abdominal pain were the most often reported terms.

Conclusion(s)

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