OBSERVATIONAL STUDY REPORT SYNOPSIS

Patient Registry of Roflumilast In Real Life-Division of North Asia - an observational, non-comparative, prospective cohort study, in patients with COPD treated with Roflumilast (Daxas®) in Asia

Milestones:

Milestone	Date
Clinical Study Protocol	July 2012
First Subject In	Dec 2014
Last Subject In	Sep 2015
Last Subject Out	Aug 2016
Database Lock	Oct 2016
Stats Report	Dec 2016
Clinical Study Report	Feb 2017

Phase of development: Not Applicable – Observational study

Sponsor: AstraZeneca AB

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

Background/Rationale:

Chronic obstructive pulmonary disease (COPD) is a major global health issue given its increasing incidence, and associated morbidity and mortality. The World Health Organization (WHO) estimates that approximately 80 million people worldwide have moderate to severe COPD. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally (2). Total deaths from COPD are projected to increase by >30% in the next 10 years and COPD is estimated to become the 3rd leading cause of death worldwide by 2030. Roflumilast (Daxas®) is a novel oral therapy indicated for maintenance treatment of severe COPD (3) (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 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.

A patient registry is an effective tool to capture real life data and demonstrate the performance of Roflumilast (Daxas®) in standard clinical practice.

Objectives:

- Document frequency and severity of exacerbations in patients with severe COPD during treatment with Roflumilast (Daxas®)
- Document seasonal variation of exacerbations
- Document changes in lung function during Roflumilast (Daxas®) treatment, compared to baseline lung function at study enrolment
- Document change in the dyspnoea levels using Modified Medical Research Council (mMRC) scale.
- Document changes in COPD Assessment Test (CAT) score
- Document changes in blood oxygen saturation assessed with pulse oximetry
- Document weight change during treatment with Roflumilast (Daxas®)

Study design: an observational, non-interventional, non-comparative, prospective study

Data source: Primary data collection in Hong Kong and South Korea

Study population: The study was conducted in approximately 15 sites in Hong Kong and South Korea. The observational period for each patient will be up to twelve months. Roflumilast (Daxas®), available as 500 µg film-coated tablets for once daily oral treatment. The eligibility is determined by the treating physician. Concomitant treatment is prescribed by the treating physician according to the local standards.

Inclusion Criteria:

- Signed informed consent to the data collection.
- Roflumilast (Daxas®) treatment initiated in Roflumilast (Daxas®)naïve patients with COPD at the time of registry

Exclusion criteria: There are no exclusion criteria per se. However it is expected that patients are treated according to locally approved package insert.

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). Change of variables in time were 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.

Results: Out of 132 patients included in the valid sample 75 (56.8 %) had any exacerbation from treatment start to last visit; for these patients 205 exacerbations were recorded. Median number of exacerbations during one-year follow-up was 1 exacerbation (5% - 95% percentile: 0 – 6), one year prior to treatment start 1 too (but 5% - 95% percentile was wider: 0 – 8). Out of 75 patients with any exacerbation 30 (40 %) patients have one

exacerbation and 45 (60 %) patients had more than one exacerbation during one year follow-up; out of these 45 patients 33 (73.3%) were Retiree or Pensioner. Prior to treatment start there were 93 (71 %) patients with any exacerbation; 28 (30 %) with one and 65 (70 %) with more than one exacerbation. The number of exacerbation for COPD phenotypes during one year follow-up was as follows: 2 (5% - 95% percentile: (0 - 8)) exacerbations for combined subgroup, 1 (5% - 95% percentile: (0 - 4)) exacerbation for emphysema and 0 (5% - 95% percentile: 0 - 2) exacerbation for chronic bronchitis. When comparing number of exacerbation during treatment and prior, decrease of exacerbations is the most apparent for chronic bronchitis subgroup (from 1 (0, 10) to 0 (0, 2) exacerbation). For other phenotypes decrease was less apparent (exacerbation prior to treatment was 1 (5% - 95% percentile: 0 - 5) for emphysema and, 2 (5% - 95% percentile: 0 – 9) for combined)). Results can be affected by different distribution of variables in phenotypes subgroups, but are in accordance with Daxas phenotype indication introduced in SPC, i.e. chronic bronchitis. Median time to first exacerbation is 236 days (95% CI: 144; 318 days) and for phenotypes is as follows: for emphysema phenotype 164 days (95% CI: 105; 274), for chronic bronchitis was not determined, as more than half of patients did not experience the event and for combined subgroup 287 days (95% CI: 67; 385).

Conclusion: Exacerbations are less frequent after one year of treatment with Daxas in chronic bronchitis subgroup. For other phenotypes the decrease of exacerbation is not so considerable.

Publications: To be determined