Clinical Study Report Synopsis	
Drug Substance	Roflumilast
Study Code	D7120R00003
Edition Number	1.0
Date	15 Sep 2023
EudraCT Number	EUPAS14852
NCT Number	NCT03381573

Long-term Post-marketing Observational Study of the Safety of DAXAS™ (roflumilast)

Study dates: Initial Database Contract: 23 Mar 2017
Final Analytic Dataset: 16 Sep 2022
Final Study Report: 16 Dec 2022
Final Study Report Addendum: 12 Apr 2023

Phase of development: Phase IV; Post Authorisation Safety Study

International Co-ordinating Investigator: Prof. Edeltraut Garbe (Leibniz Institute for Prevention Research and Epidemiology - BIPS, Germany)

Sponsor's Responsible Officer: PPD
AstraZeneca, Cambridge UK)

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

1. Study centres

This observational cohort study was conducted using databases in Germany (GER), Sweden (SWE), the United States (US), and Norway (NOR). Analyses for GER, SWE, and the US are presented in the Final Clinical Study Report (CSR). The results for NOR are provided as an addendum to the CSR, as they became available after submission of the Final CSR to the European Medicines Agency (EMA).

Data sources:

- For GER, the German Pharmacoepdemiological Research Database (GePaRD).
- For SWE, Swedish National Board of Health, and Welfare, allowing linkage of the Swedish Prescribed Drug Register (PDR) with the National Population Register, the Swedish Cause of Death Register, the Swedish Cancer Registry, and registries holding socio-demographic data.
- For the US, the Military Health System (MHS) nationwide managed care program (TRICARE) that combines healthcare claims from the US Department of Defense facilities with those from the private sector.
- For NOR, the National Population Register held by the Tax Administration; the Norwegian Patient Register held by the Norwegian Directorate of Health; the Cancer Registry of Norway held by the Oslo University Hospital Trust; the Norwegian Cause of Death Registry and the Norwegian Prescription Database held by the Norwegian Institute of Public Health.

2. Publications

None at the time of writing this report.

3. Objectives and Outcomes

Objective: The main objective of this study was to evaluate the long-term safety of roflumilast in the treatment of COPD, with the main focus on 5-year all-cause mortality and to evaluate potential safety issues identified during the development programme of roflumilast.

Outcomes: The primary outcome in the study was 5-year all-cause mortality. All-cause mortality without restriction of follow-up was an additional outcome.

Other secondary outcomes were death by suicide or hospitalisation for suicide attempt, hospitalisation for any cause, hospitalisation for major cardiovascular events, respiratory disease-related hospitalisation, new diagnosis of depression, new diagnosis of malignant neoplasm, hospitalisation due to serious diarrhoea of non-infectious origin, abnormal and

unexplained weight loss, and new diagnosis of tuberculosis or hepatitis B or C or other severe viral hepatitis infection (except hepatitis A).

4. Study design

This final report and its accompanying addendum describe a multi-country, non-interventional post authorization safety study using patient-level secondary data from databases from four countries (GER, SWE, US and NOR).

Patients with chronic obstructive pulmonary disease (COPD), aged 40 years or older and with a first-time exposure to roflumilast were compared to unexposed COPD patients (i.e., not exposed to roflumilast, also called "controls"). Exposed patients were matched with up to 5 unexposed patients on propensity score (PS), age, sex, and cohort entry date (CED). PS matching was used to make the exposed and unexposed population as comparable as possible. For the exposed cohort, the CED of each patient was defined as the date of the first dispensation of roflumilast. For the matched controls, the CED of each patient was defined as the same date as that of the corresponding exposed patient in SWE, US, and NOR. In GER it was only feasible to perform matching by month and not by day. In GER the CED of unexposed patients was set to be on the 15th of the month of cohort entry of the exposed matched patient.

This study included 3 annual cohorts of COPD patients, with the first cohort identified in 2011 and subsequent cohorts created for patients who began roflumilast treatment in 2012 and 2013. Each annual cohort was longitudinally followed for at least 5 years. Follow-up for the whole study ended when the last patient of the last of the annual cohorts contributing to the minimum of 2000 roflumilast-exposed patients reached the minimum 5-year follow-up, except in NOR where total sample size of exposed patients was 1642.

5. Target subject population and sample size

The study population consisted of 50567 (8783 exposed to roflumilast) patients in GER, 19025 (3234 exposed to roflumilast) patients in SWE, 56792 (9598 exposed to roflumilast) patients in the US and 9472 (1624 exposed to roflumilast) patients in NOR.

6. Statistical methods

After matching of roflumilast-exposed patients to non-exposed controls, using conventional PS or high dimensional propensity score (HDPS) (for sensitivity analyses), crude mortality for the primary endpoint and incidence rates of other endpoints were calculated and compared between roflumilast exposed and unexposed COPD patients. Cox models were used to estimate crude and adjusted HRs of the primary and secondary outcomes. In addition to the analyses for the individual countries, a meta-analysis was conducted to pool effect estimates obtained from GER, SWE, US and NOR for analysis of the primary and selected secondary outcomes. In

addition, a meta-analysis was also conducted for effect estimates obtained from HDPS matched cohorts in sensitivity analysis for the primary outcome.

7. Summary of safety results

Matching on propensity score: Over 95% of roflumilast-exposed patients were matched to at least one unexposed patient in all countries. Overall, 542/50567 patients in GER, 15/19025 patients in SWE, 43/56792 patients in the US, and 18/1642 patients in NOR were roflumilast-exposed patients who were excluded since no match with similar PS could be found. Although the excluded roflumilast-exposed unmatched patients had high PS, indicating more severe COPD and therefore a higher risk of the endpoints of interest, the matched cohort included patients with almost similarly high PS as that of the most severe roflumilast-exposed unmatched patients.

After matching, the PS distribution at CE was similar in exposed and unexposed cohorts although some markers of COPD remained imbalanced with more events occurring in exposed patients (i.e., exceeded the pre-defined cut-off value for imbalance [standardized difference of 0.1]). In all countries, several other markers for COPD severity showed higher prevalence in roflumilast-exposed patients compared to unexposed patients; however, these did not exceed the pre-defined cut-off. Furthermore, after PS matching, some variables related to COPD severity showed an imbalance between exposed and unexposed cohorts when evaluated at 1 year before CED, further indicating an imperfect PS matching at baseline.

Roflumilast exposure: Many roflumilast-exposed patients were dispensed roflumilast only 1 to 3 times, accounting in each annual cohort for 50% of exposed patients or more in GER, SWE and NOR and for >40% of exposed patients in the US. On the other hand, the proportion of exposed patients with ≥10 dispensations across the annual cohorts in the 3 countries ranged from 27.5% in SWE to 39.9% in the US.

Duration of follow-up: The median follow-up (first quartile[Q1] – third quartile [Q3) was at least 1808 (Q1-Q3: 772-2276) days across cohorts in all countries:

- 2020 (Q1-Q3: 961-2584) days for never-exposed patients and 2008 (Q1-Q3: 1057-2573) days for ever-exposed patients in GER,
- 1895 (Q1-Q3: 759-2401) days for never-exposed patients and 1908 (Q1-Q3: 885-2388) days for ever-exposed patients in SWE, and
- 1877 (Q1-Q3: 760-2297) days for never-exposed patients and 1808 (Q1-Q3: 772-2276) days for ever-exposed patients in the US.
- 1844 (Q1-Q3: 716-2264) days for never-exposed patients and 1848 (Q1-Q3: 868-2276) days for ever-exposed patients in NOR

Primary outcome: After adjustments for age, sex, variables imbalanced after PS matching at cohort entry, and additional markers of COPD severity and overall morbidity the adjusted HRs for 5-year all-cause mortality comparing ever users of roflumilast vs never users, were 1.12 (95% CI: 1.08, 1.17) in GER, 0.98 (95% CI: 0.92, 1.04) in SWE, 1.16 (95% CI: 1.12, 1.20) in the US and 1.00 (95% CI: 0.92, 1.08) in NOR.

Analyses by exposure status defined as current, recent, and past did not confirm an elevated risk during current use as adjusted HRs were 0.93 (95% CI: 0.88, 0.98) in GER, 0.80 (95% CI: 0.73, 0.88) in SWE, 1.00 (95% CI: 0.95, 1.04) in the US, and 0.77 (95% CI: 0.67, 0.87) in NOR. During recent and past use, an elevated mortality risk was observed in GER, US, and NOR whereas in SWE the mortality risk was elevated only during past use.

Analyses by cumulative exposure categories did not consistently show higher mortality risk with increasing exposure durations (<3 months, 3 to 12 months, >12 to 24 months, >24 months) across countries. No elevation of risk for any of the cumulative exposure duration categories was observed in SWE and NOR. In GER, a statistically significant increase of mortality risk was observed for 3 to 12 months and 12 to 24 months cumulative exposure. In the US, a statistically significant increase in risk was observed for all cumulative exposure durations, with a similar magnitude of risk in all duration categories.

Secondary Outcomes: For SWE, GER, US and NOR there was an increased risk of respiratory disease-related hospitalisation comparing current users of roflumilast with never users. Similarly, the risk for hospitalisation for any cause was higher among current compared to never users of roflumilast.

Risks of new diagnosis of depression, abnormal unexplained weight loss, and hospitalisation for diarrhoea were statistically significantly higher in current roflumilast users than never users in at least 1 country.

A statistically significant increase of the risk of any malignancy (using latency periods of 0, 1 and 2 years) was observed in GER and the US, mainly driven by solid tumours. In SWE, there was no statistically significant risk of any malignancy for no latency period and 2 years latency. In NOR there was no statistically significant increase of the risk of any malignancy observed (using latency periods of 0, 1 and 2 years). Cancer registry data from SWE and NOR (not available in other countries) showed that the most frequent new malignancies were primarily neoplasms of bronchus and lung, (which accounted for 31.9% of events in exposed patients and 27.5% in unexposed patients in SWE; and 41.8% of events in exposed patients and 34.2% in unexposed patients in NOR) and neoplasms of the digestive organs (which accounted for 28.6% of events in the exposed patients and 22.7% of events in the unexposed patients in SWE; and 19.0% of events in the exposed patients and 25.7% of events in the unexposed patients in NOR).

Meta-analysis: There was considerable between-country heterogeneity (I2 = 90%) in the meta-analysis of the results of roflumilast use (ever versus never) and association with 5-year all-cause mortality. Results from GER and the US showed a slightly increased 5-year mortality for ever versus never use, while there were no indications of increased mortality in SWE and NOR. Due to the presence of this degree of heterogeneity which hampers interpretation of outputs from the meta-analysis, the results of meta-analysis are only presented for completeness.

8. Conclusion

The results of this final report and its accompanying addendum confirm and expand preliminary evidence in the interim reports for the primary and secondary outcomes. After adjustment for known and measurable confounding, a small but statistically significant increase of risk of 5-year all-cause mortality associated with ever use of roflumilast versus never use was observed in GER and the US but not in SWE or NOR. This marginal increase of mortality risk is most likely due to residual confounding and informative censoring/selection bias over time.

Descriptive and analytical findings indicate that PS matching reached imperfect balance at baseline and deteriorated over time during the follow-up period of this study. As an alternative approach to conventional PS matching and to further address the presence of residual confounding, HDPS matching was performed by empirically selecting proxies for unmeasured confounders. Whilst effect estimates from the HDPS models were slightly attenuated towards the null, this methodology was insufficient to completely eliminate the presence of residual and unmeasured confounders.

Analyses to address the main study aim to evaluate the long-term safety of uninterrupted use of roflumilast did not demonstrate a consistent increase in mortality with increasing roflumilast exposure to >24 months in all study countries.

An increased risk was observed for respiratory disease-related hospitalisations and all-cause hospitalisation in all 4 countries that is likely due to confounding by indication, informative censoring/selection bias over time, and important missing variables such as FEV1 and smoking. However, no new risks compared with those that already emerged in the clinical development programme were observed. The excess risk of depression, diarrhoea, and weight loss are in line with clinical trial findings. The investigation of cancer risk was hampered, amongst others, by the lack of complete smoking data. In GER and the US, adjusted HRs showed slightly elevated risk estimates for any malignancy with statistical significance for ever use of roflumilast irrespective of the latency assumption used (no latency, 1-year or 2- years latency). However, the increase in risk was not significantly elevated for no latency and 2-years latency and borderline significant for 1-year latency assumption in SWE where data are derived from a cancer registry with better data quality (in comparison to GER and the US which are based on claims data). In NOR the risk of cancer was not significantly elevated for any latency category.