PASS Study Report	
Active substance	R03DX07 Roflumilast
Product reference	EMEA/H/C/001179; PASS study code ID: D7120R00003
Version number	1.0
Date	14 December 2022

Long-term Post-marketing Observational Study of the Safety of DAXAS™ (roflumilast) - Combined Results of Data from Sweden, Germany, and the United States - Final Report

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB, SE-151 85 Södertälje, Sweden
MAH contact person	PPD
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Approved by: PPD

Principal Investigator

Date

PASS INFORMATION

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Procedure number	*Not applicable*
Marketing authorisation holder	AstraZeneca AB
Joint PASS	No
Research question and objectives	The main objective of this study is to evaluate the long-term safety of Daxas™ (roflumilast) in the treatment of chronic obstructive pulmonary disease (COPD) with the main focus on 5-year all-cause mortality. In addition, the study will evaluate potential risks, including potential safety issues identified during the development programme of roflumilast.
Countries of study	Germany, Sweden, United States, Norway
Author	Prof. Edeltraut Garbe

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1. ABSTRACT

Title

Long-term post-marketing observational study of the safety of roflumilast

Keywords

Roflumilast, Chronic Obstructive Pulmonary Disease (COPD), Chronic Bronchitis, Drug Safety, Exacerbations, Mortality

Rationale and background

Roflumilast is licensed (i) for maintenance treatment of severe COPD (FEV_1 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 (EU) and (ii) as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (US). At the time of approval, a total of 2874 COPD patients had been treated with roflumilast in clinical trials of 12-month duration, but clinical trials of longer duration had not been conducted. As a condition of approval for marketing in the EU, the EMA requested the MAH to conduct a long-term comparative observational safety study.

Research question and objectives

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.

Study design

An observational cohort study was conducted using databases in Germany, Sweden, the United States, and Norway.

Patients with COPD, aged 40 years or older and with a first-time exposure to roflumilast were compared to unexposed COPD patients (ie, not exposed to roflumilast, also called “controls”). Exposed patients were matched with up to 5 unexposed patients on PS, age, sex, and 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 and the US. 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.

Setting

Electronic healthcare databases in GER, SWE, the US, and NOR holding demographic data, data on health, including death status, and dispensing of medications.

Subjects and study size

The source population consisted of ≥ 40-year-old COPD patients who had or had not been exposed to roflumilast. The study population consisted of 50567 (8783 exposed to roflumilast) patients in GER, 19025 (3234 exposed to roflumilast) patients in SWE, and 56792 (9598 exposed to roflumilast) patients in the US.

Variables and data sources

***Exposure variable*:** Exposure to roflumilast was ascertained based on the presence of dispensed prescriptions in the relevant databases**.** Roflumilast exposure was categorized as "ever used" vs "never used" for the primary analysis. Time-varying exposure was also defined as current, recent, and past use; and by cumulative duration of use. Exposure (risk) time was classified as "Current use" if a roflumilast exposure period was on-going or ended in the last 1 to 5 days; "Recent use" if the most recent roflumilast exposure period ended within 6 to 60 days; "Past use" if the most recent roflumilast exposure period ended over the last 60 days. An extension of exposure corresponding to 50% of the last dispensed duration was included in the definition of exposure to account for any intake interruption. As with any estimate of drug exposure, there is a margin of error with this method and some uncertainty about the exact endpoint of drug exposure. Cumulative duration of use was defined as <90 days, 90 to 365 days, >365 days. As part of a sensitivity analysis, the last category was further divided into 366 to 730 days and >730 days.

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).

***Other covariates*:** Characterisation of baseline therapy, baseline medical history and other socio-demographic covariates.

Data sources:

- For GER, the GePaRD.
- For SWE, Swedish National Board of Health and Welfare, allowing linkage of the Swedish 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 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 NorPD held by the Norwegian Institute of Public Health.

Statistical Methods

After matching of roflumilast-exposed patients to non-exposed controls, using conventional PS or 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, and the US 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.

Results

The results presented here, and the rest of the study report are for GER, SWE, and the US. At the time of the final study report, results from NOR were unavailable. Outputs from NOR will be provided as soon as they become available.

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, and 43/56792 patients in the US 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 severity (number of hospitalisations due to COPD exacerbation in the 30 days and 12 months before CED) remained imbalanced with more events occurring in exposed patients (ie, exceeded the pre-defined cut-off value for imbalance [standardized difference of 0.1]). Other markers of COPD severity that remained imbalanced were the number of emergency room visits due to COPD in the last 30 days before cohort entry, the number of moderate COPD exacerbations in the last 12 months before CE and SABA use in the last 4 months before cohort entry. 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 and SWE 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 was at least 1808 days (4.9 years) 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.

Primary outcome: In all countries, the 5-year all-cause mortality risk for ever-versus-never exposure to roflumilast was elevated in roflumilast-treated patients, with crude HRs of 1.17 (95% CI: 1.13, 1.22) in GER, 1.11 (95% CI: 1.05, 1.18) in SWE, and 1.25 (95% CI: 1.21, 1.29) in the US. Adjustments for age, sex, variables imbalanced after PS matching at cohort entry, and additional markers of COPD severity and overall morbidity, resulted in reduced adjusted HRs of 1.12 (95% CI: 1.08, 1.17) in GER, 0.98 (95% CI: 0.92, 1.04) in SWE, and 1.16 (95% CI: 1.12, 1.20) in the US.

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, and 1.00 (95% CI: 0.95, 1.04) in the US. During recent and past use, an elevated mortality risk was observed in GER and the US, 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. 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.

The robustness of the main analysis for the primary outcome of mortality was evaluated in several sensitivity analyses that varied the assumptions regarding exposure, outcome, and potential sources of bias:

- Accounting for the possibility that events may occur several months after exposure cessation, follow up time for current exposure was censored after first discontinuation. In this sensitivity analysis, all adjusted HRs comparing the exposed to the unexposed cohort, for each of the cumulative exposure categories in SWE and the US were below 1. These results were statistically significant except for the cumulative exposure category of >24 months which was not statistically significant. For exposure durations of >24 months,

the adjusted HRs were 0.98 (95% CI: 0.80, 1.21) in SWE and 0.95 (95% CI: 0.84, 1.08) in the US. The analysis was not conducted in GER.

- Analyses stratified by the number of roflumilast dispensations throughout follow-up did not demonstrate a consistent increase of mortality with increasing roflumilast exposure. There was a significant increase in mortality risk for 1 dispensation in all countries, for 2 to 3 dispensations in GER and the US only, for 4 to 9 dispensations in all countries, and for ≥ 10 dispensations in GER only. In SWE and the US, the mortality risk was reduced for ≥ 10 dispensations of roflumilast compared to never use.
- In the HDPS-matched patients, the adjusted mortality risk was consistently higher in the roflumilast-exposed cohort compared to the unexposed cohort in each country, with a statistically significantly elevated HR in GER and the US. The adjusted HRs were, however, numerically lower than in the analyses using conventional PS matching.

Secondary outcomes: For SWE, GER, and the US 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. The adjusted HRs for new diagnosis of solid tumour with no latency, in ever-versus-never exposure to roflumilast were 1.11 (95% CI: 1.05, 1.17) in GER, 1.03 (95% CI: 0.94, 1.14) in SWE and 1.04 (95% CI: 0.98, 1.11) in the US. Estimates did not change substantially with 1 or 2 years of latency. Cancer registry data from SWE (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) 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).

Meta-analysis: There was considerable between-country heterogeneity ($I^2 = 92\%$) in the meta-analysis of the results of roflumilast use (ever versus never) and association of 5-year all-cause mortality. Results from GER and the US showed a slightly increased 5-year mortality risk while results from SWE showed a non-significant beneficial effect. 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.

Conclusion

The results of this final report 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. 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 3 countries that is likely due to confounding by indication, informative censoring/selection bias over time, and important missing variables such as FEV_1 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).

At a request from the EMA, a meta-analysis was conducted for 5-year all-cause mortality. Results showed substantial between-country heterogeneity with increased mortality risks in two countries (GER and the US) and largely no elevated risks, and even some protective effects, in SWE. Since this heterogeneity cannot be solved by statistical methods (eg, by random effects models), it was decided to only present the country-specific results in the Abstract and not the results of the meta-analysis (which are presented in the Study Report for completeness). In contrast to GER and the US, where data availability before CED was limited to 1-2 years, there was long data availability before CED in SWE which made it possible to include the variable “duration of COPD” into the PS model. Since “duration of COPD” is an important marker of COPD severity, inclusion of this variable into the PS model presumably achieved better balance between the exposed and unexposed cohort with respect to COPD severity, possibly explaining the discrepancies in the results between SWE and GER/US.

Marketing Authorisation Holder(s)

AstraZeneca AB, Sweden

Names and affiliations of principal investigator

Prof. Edeltraut Garbe (Leibniz Institute for Prevention Research and Epidemiology - BIPS, Germany)

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	anatomical, therapeutic and chemical
CE	cohort entry
CED	cohort entry date
CI	confidence interval
COPD	chronic obstructive pulmonary disease
DDD	defined daily dose
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FEV_1	Forced expiratory volume in 1 second
GePaRD	German Pharmacoepdemiological Research Database
GER	Germany
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPI	generic product identifier
HDPS	high-dimension propensity score
HR	hazard ratio
ICD-9	International Classification of Diseases and Related Health Problems, 9th Revision
ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-GM	International Classification of Diseases and Related Health Problems, 10th Revision, German Modification
ICS	inhaled corticosteroid
IR	incidence rate
IRR	incidence rate ratio
ITT	intent-to-treat
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
MAH	Marketing Authorisation Holder(s)
MHS	Military Health System
MR	mortality rate
MRR	mortality rate ratio
NDC	National Drug Code
NOR	Norway
NorPD	Norwegian Prescription Database
NPR	National Patient Register
PASS	post-authorisation safety study
PDR	Prescribed Drug Register
PRAC	Pharmacovigilance Risk Assessment Committee
PS	propensity score

Abbreviation or special term	Explanation
RCT	randomised controlled trial
SABA	short-acting β_2-agonist
SAMA	short-acting muscarinic antagonist
SAP	statistical analysis plan
SD	standard deviation
SHI	statutory health insurance
SmPC	Summary of product characteristics
SWE	Sweden
TIS	treatment intensity score
US	United States
VHA	Veterans Health Administration

3. INVESTIGATORS

The Principal Investigator for this study is Professor Edeltraut Garbe, MD, MSc Epidemiology and Biostatistics, PhD, Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany.

The following investigators are local Principal Investigators:

Country	Investigators	Study centre
Germany	PPD	Leibniz Institute for Prevention Research and Epidemiology - BIPS
Sweden	PPD	IQVIA, Global Database Studies
US	PPD	IQVIA Real World Evidence Solutions, Epidemiology and Drug Safety
Norway	PPD	UiT the Arctic University of Norway

4. OTHER RESPONSIBLE PARTIES

The following investigators are members of the Independent Scientific Advisory Committee:

Member	Area of Expertise	Institute
Edeltraut Garbe (Chair)	Pharmacoepidemiology	BIPS, Germany
PPD	Epidemiology, Statistics	BIPS, Germany
PPD	Biostatistics	IQVIA, Global Database Studies, Finland
PPD	Medical	Uppsala University, Sweden

The following responsible parties were involved in the conduct of the study but are not listed as investigators:

Country	Responsible party	Study centre
Germany	PPD (Epidemiologist)	Leibniz Institute for Prevention Research and Epidemiology - BIPS
Germany	PPD (Statistician)	Leibniz Institute for Prevention Research and Epidemiology - BIPS
Sweden	PPD (Statistician)	EPID Research
Sweden	PPD (Statistician)	EPID Research
Sweden	PPD (Statistician)	EPID Research
Sweden	PPD (Statistician)	IQVIA Global Database Unit
Sweden	PPD (Statistician)	IQVIA Global Database Unit
Sweden	PPD (Statistician)	IQVIA Global Database Unit
US	PPD (Epidemiologist)	IQVIA Real World Evidence Solutions
US	PPD (Epidemiologist)	IQVIA Real World Evidence Solutions
US	PPD (Statistician)	IQVIA Real World Evidence Solutions
US	PPD (Statistician)	IQVIA Global Database Unit
US	PPD (Statistician)	IQVIA Global Database Unit

5. MILESTONES

The following milestones have been planned and/or met:

Milestone	Planned date	Actual date	Comments
Start of data collection	31 October 2013	15 December 2013	
End of data collection	31 January 2020	16 September 2022	
Registration in the EU PAS register	---	9 September 2016	EU PAS Register No: EUPAS14852
First interim report	31 April 2017	31 October 2017	Actual date different from planned due date to project on hold from change of study sponsor.
Second interim report	30 June 2018	25 June 2018	Actual date aligned with PRAC procedural timetable
Third interim report	30 June 2019	25 June 2019	Actual date aligned with PRAC procedural timetable
Final report of study results	31 December 2022	14 December 2022	Results for Norway will be reported separately when available

6. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease is a leading cause of death. Takeda A/S received central marketing authorisation in the EU in July 2010 and regulatory approval in Canada in November 2010 for its selective phosphodiesterase-4 inhibitor DAXAS™ (roflumilast) for maintenance treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment (Daxas SmPC 2011; Daxas Product Monograph 2011). In the US, DALIRESP™ (roflumilast) was approved on 28 February 2011 by the Food and Drug Administration as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. In the EU, DALIRESP and LIBERTEK were duplicate licenses of DAXAS (EU/1/10/636, EMEA/H/C/001241) as per Article 82 of the Regulation No 726/2004. On 11 January 2018 those licenses were withdrawn due to commercial reasons, not related to any quality or safety issue.

Roflumilast is available as 500 µg tablets, and the recommended dose is one 500 µg tablet once daily. During the study, roflumilast also became available as a 250 µg starting dose for the first 4 weeks of treatment in some countries. Roflumilast was first launched in Germany and Denmark (August 2010), followed by Sweden and Canada in December 2010, and the United States in May 2011. The 250 µg dose was approved in the US on 23 January 2018 and in the EU on 23 April 2018. Roflumilast is contraindicated in patients with hypersensitivity to the tablet ingredients and in patients with moderate to severe liver impairment (Child Pugh B or C).

At the time of initial Marketing Authorisation Application, a total of 2874 COPD patients had been treated with roflumilast in clinical trials of 12 months' duration. However, clinical trials of longer duration had not been conducted. Since roflumilast is licensed as a permanent maintenance treatment, a long-term safety assessment exceeding 12 months was requested as a condition for approval in the EU. During the approval process, Takeda A/S as the MAH of roflumilast at that time therefore committed to the EMA to perform a database PASS to evaluate the long-term safety of roflumilast in the treatment of COPD in large, unselected COPD populations, with focus primarily on 5-year all-cause mortality. Additionally, secondary and exploratory objectives of the study were to evaluate potential risks, including potential safety issues identified during the development programme of roflumilast. On 16 November 2016, AstraZeneca took over as MAH from Takeda A/S and became the sponsor of this PASS.

On 31 October 2017, the first interim report of the PASS was submitted to the EMA. A revised first interim report, addressing questions from the PRAC, was submitted on 05 March 2018. In response to the revised first interim report, the EMA requested AstraZeneca conduct additional analysis including the addition of data from other Nordic countries, use of HDPS models and meta-analysis for the final report. In addition, the EMA requested AstraZeneca re-analyse the data using additional definitions of exposure (current, recent past up to 3 months, up to 12 months and more than 12 months as opposed to ever versus never which was used in the first interim report).

On 25 June 2018, the second interim report was submitted. The final PRAC assessment and CHMP conclusions of the second interim report (received in August 2018) concluded that the risk-benefit balance of medicinal products containing roflumilast was unchanged. However, additional clarifications on the interpretation of the results were requested for the third interim report.

The third interim report was submitted on 25 June 2019. During assessment of the third interim report, PRAC concluded that the risk-benefit balance of medicinal products containing the active substance roflumilast remained unchanged. However, additional clarifications were required for the final report. These clarifications included report of outputs using the HDPS model, presentation of results from Norway and results from additional analyses.

AstraZeneca submitted variations for extension of the final study report submission due date in order to complete the additional analysis requested by the EMA, including the use of data from Norway. AstraZeneca received agreement from the EMA to submit the final study report on 31 December 2022. In September 2022, AstraZeneca contacted EMA regarding challenges with obtaining access to the Norwegian data and the risk of the delay affecting AstraZeneca's ability to meet the final CSR submission timeline of 31 December 2022. In response the EMA advised that the timeline for final CSR submission in December 2022 be maintained, and if outputs from the Norwegian data were still unavailable or contained serious errors at that time, they should be omitted from the final CSR. However, the EMA advised that if the Norwegian outputs did become available during the assessment procedure, they would welcome its submission.

This final report presents the planned analyses through the end of study follow-up, which was defined as the time when the last noncensored patient in the established cohorts completed the 5-year follow-up period. This final report includes the results of all planned analyses for cohorts in the GER, SWE, and the US databases. At the time of the final study report, results from NOR were unavailable. Outputs from NOR will be provided as soon as they become available.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study was to evaluate the long-term safety of roflumilast in the treatment of COPD, with 5-year all-cause mortality as primary outcome.

The secondary objective of the study was to evaluate potential risks identified during the clinical trials of roflumilast as secondary outcomes. Specifically, this study aimed to compare the incidences of 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, abnormal and unexplained weight loss, hospitalisation due to serious diarrhoea of non-infectious origin, and new diagnosis of tuberculosis or hepatitis B or C or other severe viral hepatitis infection (except hepatitis A) in roflumilast treated (“exposed”) COPD patients compared with matched COPD patients not treated with roflumilast (“unexposed”).

The exploratory objectives of the study were to evaluate the association between roflumilast exposure and cause of death, including cardiovascular disease related death, respiratory disease related death, cancer death, and other causes of death in countries where such data were available.

8. PROTOCOL AMENDMENTS AND UPDATES

No amendments or updates to the protocol were made since the third interim report. The latest version of the protocol is Version 3.0 (dated 07 February 2017).

Amendments and updates included in the protocol version 2.4 (31 July 2013) and in the version 3.0 (7 February 2017) are summarised below:

- Section 8, addition of section related to exposure definitions with more detail regarding definition of duration of exposure and cumulative exposure
- Sections 11.1.3.1 & 11.1.3.2, further description of how primary and secondary analyses will be conducted
- Across protocol, changed MAH and sponsor from Takeda to AstraZeneca (sponsor personnel change)
- Section 5.1, milestones change
- Page 1, study identification change
- Page 2, coordinating study coordinators and approvers change

9. RESEARCH METHODS

9.1 Study Design

This final report describes a multi-country, non-interventional PASS using patient-level secondary data from different databases. This cohort study allows for long-term follow-up of a large population of COPD patients to complement existing data from clinical trials. Briefly, COPD/chronic bronchitis patients > 40 years of age with new use of roflumilast ("exposed patients") were compared with matched (PS, age, sex, CED) COPD/chronic bronchitis patients without use of roflumilast ("unexposed patients").

The study was based on patient-level data from different electronic healthcare databases (as detailed in Section 9.5) from 4 countries deemed relevant based on reimbursement status and number of roflumilast-treated patients: GER, SWE, the US, and NOR. Analyses were conducted and are presented separately for each country and combined. Results from NOR are not included in this final study report, and will be submitted as soon as they become available.

This study includes 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. In GER, the study period began on 01 August 2010 (the date of market launch of roflumilast in GER), but data from 2010 were insufficient to be analysed separately and were analysed together with the 2011 cohort data. For simplicity, all data collected from 01 August 2010 through 31 December 2011 in GER are referred to as "2011" in this report.

As specified in the protocol, an interim analysis was performed 2 years after extraction of the annual cohort with a minimum sample size of 2000 roflumilast-exposed patients in the respective database. Results of the analysis were presented in the first interim report. Further interim analyses were performed after 3 and 4 years and were presented in the second and third interim reports. This current report, the final study report, presents analyses using a longer follow-up period than previous interim reports (Table 1).

Table 1 Study Cohort Composition for the Interim and Final Reports

Study cohort by country	Time frame for cohort entry	End of follow-up date at interim and final report				Final report follow-up time
		First interim report	Second interim report	Third interim report	Final report	
GER[a]	2011-2013	31 Dec 2013	31 Dec 2015	31 Dec 2016	31 Dec 2018	5 y to 8 y 5 mo
SWE[b]	2011-2013	31 Dec 2014	31 Dec 2015	31 Dec 2017	31 Dec 2018	5 y to 8 y
US[c]	2011-2013	31 Mar 2016	31 Mar 2016	31 Dec 2017	31 Dec 2018	5 y to 7 y 8 mo

[a] GER 2011 cohort also includes patients who started treatment since August 2010, when roflumilast was first available in the country

[b] Roflumilast launch in Sweden was in December 2010

[c] Roflumilast launch in the US was in May 2011

GER = Germany; mo = months; SWE = Sweden; US = United States; y = years

9.2 Setting

Electronic healthcare databases holding demographic data, health data, and data on prescribing or dispensing of medications were evaluated in multiple countries in the EU, and from the military databases in the US.

Lack of reimbursement or restricted reimbursement in a given region limits the number of exposed patients and introduces bias in prescribing and dispensing. To avoid extraction of too small and/or biased cohorts from which no solid information can be derived, the protocol specified that first matched cohorts in a given region should only be established when:

1 Roflumilast had received reimbursement in the region, and/or
2 Roflumilast sales figures in the region indicated that at least 2500 individuals had been exposed after granting of reimbursement, and
3 A preliminary extract of the number of exposed individuals confirmed the availability of data for at least 2000 individuals with first prescription after granting of reimbursement.

According to these rules, data sources were selected for inclusion if reimbursement of roflumilast had been granted in the region and the number of roflumilast-treated patients captured in that region was considered sufficient for timely results with sufficient statistical power for the primary outcome to be analysed in each country/database on its own. As detailed in the first, second, and third interim reports of the study, GER, SWE, and the US, were chosen for inclusion based on these factors. Other countries were excluded due to insufficient number of roflumilast-exposed patients (The Netherlands, The United Kingdom, Canada, Denmark, Finland) and/or restricted reimbursement status of roflumilast (Norway, Denmark, Finland). In response to the regulatory review and comments to the first interim report to include Norway, data from Norwegian registries was obtained. However, access to the accurate data was not obtained in time for inclusion in this report, therefore results from Norway will be presented separately, when they become available.

The specific data sources selected as relevant and used in this multicountry study are described in more detail in Section 9.5.

Subjects, described in detail in Section 9.3, were identified on a yearly basis starting from 2011 until 2013. Subjects were followed up as described below in Section 9.3.5.

9.3 Subjects

The study population consisted of COPD/chronic bronchitis patients aged 40 years and older who had been exposed to roflumilast (exposed cohort) and a matched roflumilast unexposed cohort (unexposed cohort) that was created for comparison of the safety outcomes. All patients with at least 1 new dispensing of roflumilast were assigned to the exposed annual cohort with the CED starting on the day of roflumilast dispensation. During patient follow-up, patients may switch from unexposed to exposed. Therefore, exposed patients could have served as unexposed controls for the exposed in previous interim reports.

Roflumilast use was based on dispensations in all 4 countries.

Definitions for COPD/chronic bronchitis patients are shown below in Table 2 for each country.

Table 2 Definitions for COPD/Chronic Bronchitis Patients Used in This Multicountry Study

Diagnosis codes for COPD/chronic bronchitis		Proxy drugs (for COPD/chronic bronchitis diagnosis)		
GER, SWE	**US**	**GER[a]**	**SWE[b]**	**US[c]**
ICD-10 J44 ICD-10 J41-J42	ICD-9-CM 491.xx, 492.xx, 496.xx	ATC codes: R03BB01, R03BB04, R03BB05, R03DX07	ATC codes: R03BB01, R03BB04, R03BB05, R03BB06, R03AL02, R03AL03, R03AL04	Select GPI codes: 2210x, 2220x, 441000x, 442010x, 442099x, 44300020x, 44400010x, 44400015x, 44400017x, 44400030x, 44400033x, 44400036x, 44400040x, 444500x, 4991002x, 44993204x, 96445009x, 96445070x, 96448212x, 96488848x, 96526465x, 96527054x, 96568811x, 96645065x, 96665070x, 96667040x, 96807627x

[a] Evaluated prior to or at the CED

[b] Evaluated prior to CED

[c] Evaluated prior to or at CED (ever users) or prior to CED (never users)

ATC = anatomical, therapeutic and chemical; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; GPI = generic product identifier; ICD = International Classification of Diseases and Related Health Problems; SWE = Sweden; US = United States

9.3.1 Annual Exposed Cohort

The following inclusion criteria applied:

- Were to have 1 or more dispensations of roflumilast (ATC code R03DX07 [GER, SWE, NOR] or GPI code 44450065x [US]) with the date of first dispensation occurring during the calendar year. The date of first dispensation was defined as the CED.
- Were to be at least 40 years old at CED (SWE, US, NOR) or at least 40 years old at beginning of the respective CE year (GER)
- Were to have an inpatient or outpatient diagnosis of COPD or chronic bronchitis (GER, SWE, US) or intake of proxy drugs for such indication based on dispensation data (as indicated in Table 2) any time at (GER, NOR, US) or prior to (GER, SWE, US) the CED. In SWE, patients having an asthma diagnosis (ICD-10 J45) and no COPD diagnosis were not included based on the intake of proxy drugs
- Were required to have continuous enrolment in the respective databases for at least 1 year prior to CED (GER, SWE, US).

9.3.2 Annual Unexposed Cohort

All CEDs of the annual exposed cohorts were potential CEDs for the unexposed controls. Each patient in the unexposed cohort selected as a match (as described in Section 9.3.7) was

assigned the CED of the matched exposed patient (see Section 9.3.3). Patients meeting the following inclusion criteria for at least 1 potential CED belonged in the unexposed cohort and were eligible as matched unexposed controls:

- Had no dispensations of roflumilast prior to or during the ongoing calendar year
- Were at least 40 years old at CED (SWE, US, NOR) or at least 40 years old at beginning of the respective CE year (GER)
- Had an inpatient or outpatient diagnosis of COPD or chronic bronchitis or intake of proxy drugs for such indication based on dispensation data (as indicated in Table 2 any time prior to the CED). In SWE, patients having asthma diagnosis (ICD-10 J45) and no COPD diagnosis were not included based on the intake of proxy drugs
- In US, GER, and SWE, patients were required to have continuous enrolment for at least 1 year prior to CED.

Any matched unexposed control who at some point during the study obtained a dispensation of roflumilast was censored (as unexposed) the day before the first roflumilast dispensation. If this happened during 2011, 2012, or 2013 and they, at this point, met the inclusion criteria for the exposed cohort, they were assigned to that annual cohort with a CED corresponding to the date of their first roflumilast dispensation. Controls who switched to the exposed cohort were not replaced since up to 5 controls were selected for each exposed patient and the reduction in study power by removing a patient from the control group in this situation is very small. Controls who obtained a dispensation of roflumilast at some point after 2013 were similarly censored as unexposed the day before the first roflumilast dispensation (but were not studied as exposed in any cohort since no new cohorts were established after 2013).

9.3.3 Cohort Entry Date

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 and the US. In GER it was only feasible to perform matching by month and not by day. In GER the CED of unexposed patients was set as the 15th of the month of CE of the exposed matched patient.

9.3.4 Baseline Observation Period

Baseline therapy, baseline medical history, and baseline covariables, including proxies for severity of COPD and other known determinants of mortality and secondary outcomes, were characterised at CED with a minimum of 1-year database membership (GER and the US). The ascertainment of chronic comorbidities was based on the time periods indicated in Table 7.

9.3.5 End of Follow-up

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.

9.3.6 Censoring of Follow-up

Date of death was used as a censoring event in the analysis of secondary outcomes, and as an endpoint for the primary outcome analyses. Data were analysed up to each first outcome event (secondary outcome analyses), with follow-up time censored at the time of the first outcome.

For time-to-event analyses and for calculation of event rates involving person-time, patients were censored on the earliest date that any of the following circumstances occurred:

- Death (except when death was the outcome event under analysis)
- End of study
- For patients in the unexposed cohort who started roflumilast treatment: day before first roflumilast dispensing date
- End of insurance period (GER, US), with follow-up extended by 1 month after enrolment ended to account for 1-month administrative lag (US)
- Interruption of insurance for more than 3 days (GER)
- Emigration (SWE).

Note that additional censoring criteria were used for the exploratory analysis of cause-specific death (eg, when death related to cardiovascular disease was the outcome event of interest, patients experiencing death not related to cardiovascular disease were censored at that time).

9.3.7 Matching

The matching between exposed and unexposed was based on sex (male/female), age (±1 year) at cohort entry, exact calendar year of CE (2011/2012/2013), and PS (described below).

9.3.7.1 Propensity score

A tailored PS was developed for each annual cohort. PS modelled the likelihood among COPD patients of receiving roflumilast at each potential CED. For calculating the PS, 12 potential time points per year (1 per month) were selected for the unexposed. All CEDs of the exposed were potential CEDs for the unexposed and were assigned to the unexposed after matching. The model for the PS included the variables listed in Table 7, which cover baseline demographics, markers for COPD disease severity such as treatment intensity, exacerbations or hospitalisations for COPD or other variables related to COPD severity, baseline comorbidities and concomitant medications indicating risk factors for the primary and secondary outcomes, vaccinations, contraindications for roflumilast, and lifestyle measures.

9.4 Variables

9.4.1 Outcomes

Outcomes of interest were defined as in Table 3.

Table 3 Outcome Variables With Definitions and Coding

Outcome	Description
Primary outcome	
5-year all-cause mortality	• Death during the potential follow-up time. • GER: Identified via reason for discharge from hospital (inpatient deaths) or reason for end of insurance (in- and outpatient deaths). The date of death was set to the discharge date of the hospitalisation with death as the reason for discharge or end of insurance, whichever came first. • For SWE: Identified via date of death in the Cause of Death Registry • For US: Mainly identified via date of death code in the Social Security Death Index (see also Section 9.5)
Secondary outcomes	
Death by suicide or hospitalisation for suicide attempt (intentional self-harm or overdose)	• ICD-10 codes X60-X84 (SWE only), T39-T43 (SWE, GER) or X84.9 (GER only) • ICD-9 codes E950.x-E959.x, E980.x-E987.x
Hospitalisation for any cause	• First hospitalisation after CED
Major cardiovascular events leading to hospitalisation	• Arrhythmia (conduction disorders and dysrhythmias): ICD-10 codes I44, I45 or ICD-9 codes 427.9x • Myocardial infarction: ICD-10 codes I21, I22 or ICD-9 codes 410.x, 412.x • Cerebral infarction or stroke not specified as haemorrhage or infarction: ICD-10 codes I63, I64 or ICD-9 codes 430.x-431.x, 433.xx, 434.00-434.01, 434.11, 434.91, 436.x • Heart failure: ICD-10 codes I50 or ICD-9 code 428.xx • Pulmonary embolism: ICD-10 codes I26 or ICD-9 codes 415.1x, 673.8x
Respiratory disease-related hospitalisation, including hospitalisation due to COPD/chronic bronchitis exacerbation	• ICD-10 codes J09-J22, J40-J47 • ICD-9 codes 490.x-492.x, 496, 460.x-519.x, 491.21
New diagnosis of depression (with or without hospitalisation) [a]	• ICD-10 codes F32.2-F32.3, GPI code: 58x, or ICD-9 code 296.2x • GPI code 58x
New diagnosis of malignant neoplasm (except non-melanoma skin cancer) [a]	• ICD-10 codes C00-C97 excluding C44 • ICD-9 codes 140.x-208.x For stratification by solid and haematopoietic tumours: • Solid: ICD-10 codes C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C80, C97 or ICD-9 codes 140-172, 174-199 • Haematopoietic: ICD-10 codes C81-C86, C88, C90-C96 or ICD-9 codes 200-208
Hospitalisation due to diarrhoea of non-infectious origin	• ICD-10 codes K52.9, K59.1 • ICD-9 codes 787.91, 558.x
Abnormal and unexplained weight loss with no new diagnosis of malignant neoplasm within 4 months after abnormal weight loss diagnosis [a]	• ICD-10 codes R63.4 • ICD-9 codes 783.2x

Table 3 Outcome Variables With Definitions and Coding

Outcome	Description
New diagnosis of tuberculosis or of hepatitis B or C or other severe viral hepatitis infection (except hepatitis A) [a]	• ICD-10 codes A15, B16-B19 • ICD-9 codes 011x, 571.4x, 070.2x-070.9x
Exploratory outcomes - SWE only	
Cardiovascular related death	One of the following: • Sudden cardiac death: ICD-10 codes I46.1 • Death related to ischaemic heart disease: ICD-10 codes I20-I25 • Death related to heart failure: ICD-10 codes I50 • Death related to cardiomyopathy or dysrhythmia: ICD-10 codes I42 and I44/I45 • Death related to pulmonary heart disease or diseases of pulmonary circulation: ICD-10 codes I26-I28 • Cerebrovascular disease: ICD-10 codes I60-I69
Respiratory disease related death	• COPD, ICD-10 codes J44 • Lung cancer, ICD-10 codes C34 • Influenza and/or pneumonia, ICD-10 codes J09-J18 • Other acute lower respiratory infections, ICD-10 codes J20-J22 • Tuberculosis, ICD-10 codes A15 • Acute respiratory distress syndrome, ICD-10 codes J80 • Pulmonary oedema, ICD-10 codes J81 • Other interstitial pulmonary disease, ICD-10 codes J84
Cancer related death (other than lung cancer)	• ICD-10 codes C00-C97 except C34 and C44
Other cause of death	Any death excluding those causes listed as exploratory outcomes above in this table.

[a] In GER, only hospitalisations were considered since outpatient diagnoses in GER do not have an exact date but are related to a quarter of the year.

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; ICD = International Classification of Diseases and Related Health Problems; MHS = Military Health System; SWE = Sweden; US = United States

9.4.2 Exposure

The exposure definitions adopted for this study are summarised in Table 4.

Exposure to roflumilast was ascertained based on the presence of dispensed prescriptions in the relevant databases. Exposure status was calculated using dispensing information on package size and DDDs. Data on package size are available in all databases, thus informing on the number of tablets handed out in each dispensation. The DDD provides a measure of how long the drug intake would last if taken as 1 DDD per day. Roflumilast is a once daily 500 µg

tablet with a DDD of 500 µg per day. Roflumilast 250 µg tablets (half a DDD), intended to be used as a starting dose, were made available from 2018 onwards. However, as all of the exposed started roflumilast in 2011, 2012, and 2013, this starting dose was not applicable to the exposed cohort of interest in this study. Roflumilast exposure periods were defined by the calculated length of the prescription when the amount of dispensed roflumilast prescription is converted to DDD. Therefore, exposure time (ie, number of days), was defined to be equal to the number of DDDs given out in each dispensation (ie, usage of 1 DDD per day).

Roflumilast exposure was categorized as "ever used" vs "never used" for the main analyses on mortality and malignant neoplasm related outcomes.

For repeated dispensations, if there was a gap after the calculated end of the first supply (ie, no new roflumilast dispensation within the previous exposure period or following the first day after end of the exposure period), the exposure period was extended by up to 50% of the amount of the previous dispensation. The resulting final exposure periods, based on those assumptions, were used to define time-varying exposure as current, recent, and past use (Table 4); and by cumulative duration of use in sensitivity analysis. Exposure (risk) time was classified as "Current use" if a roflumilast exposure period was on going or ended in the last 1 to 5 days; "Recent use" if the most recent roflumilast exposure period ended within 6 to 60 days; "Past use" if the most recent roflumilast exposure period ended over the last 60 days. An extension of exposure corresponding to 50% of the last dispensed duration was included in the definition of exposure to account for any intake interruption. As with any estimate of drug exposure, there is a margin of error with this method and some uncertainty about the exact endpoint of drug exposure. Each patient could contribute exposure time to all 3 use categories of current, recent, and past use.

Gap Extension

As defined in the above paragraph, a gap extension of up to 50% of the duration of the exposure was added to each dispensation for which the calculated end of the dispensation was not followed by another dispensation of roflumilast covering the next day. This was done to account for delays in filling a prescription and for nonadherence. The gap extension was also applied to the last roflumilast dispensation to prevent bias (Nielsen 2008, Nielsen 2009). Sensitivity analyses considered a gap extension of 100% and no gap extension.

Cumulative Duration

Exposure throughout follow-up was stratified by days of supply (regardless of treatment interruptions). The total of DDD throughout follow-up, which in the case of roflumilast dispensing was equivalent to the total days of supply, were computed and grouped in the categories of cumulative duration of <90 days, 90 to 365 days, >365 days. As part of a sensitivity analysis, the last category was further divided into 366 to 730 days and >730 days. As cumulative use was estimated based on DDD dispensed, the gap extension did not apply to the definition of these categories. Each patient could contribute to multiple groups. The analyses of the primary outcomes compared each of the strata of cumulative day supply to never use.

Table 4 Exposure Variables

Variable	Description	Categories
Roflumilast		
"Ever use"	Time-varying variable, which has status "Never" at all times prior to the first roflumilast dispensation and "Ever" at all times thereafter	• Never • Ever
"Use status"	Time-varying variable, which has status "Never" at all times prior to the first roflumilast dispensation, "Current use" if roflumilast exposure period is on-going or has ended within 1-5 days; "Recent use" if the most recent roflumilast exposure period has ended within 6-60 days; "Past use" if the most recent roflumilast exposure period has ended since over 60 days	• Never • Current use • Recent use • Past use
"Cumulative duration"	Time-varying variable, which has initial value 0 days, (equivalent to 0 DDDs) at all times prior to the first roflumilast dispensation, and from the first dispensation onwards is equal to the total number of dispensed DDDs before the outcome date. Prior to analyses, the calculated continuous values were categorised as: 'Never', 'Under 90 days', '90 to 365 days', 'Over 365 days', '366-730 days', and 'over 730 days', which measure cumulative duration	• Never • Under 90 days • 90 to 365 days • 366 to 730 days • Over 730 days
"Time since discontinuation"	Time-varying variable, which has value "Not applicable" at all times prior to the first roflumilast exposure and value "Concurrent use" if roflumilast exposure is ongoing. After each roflumilast exposure period (including gap extension), the value is counted as the days from the outcome date to the end of the exposure period closest in time. In the analyses, the calculated continuous values were categorised as: "Under 90," "90-365," "Over 365" which measure days since discontinuation	• Not applicable • Concurrent use • Under 90 days • 90 to 365 days • 366 to 730 days • Over 730 days
Other drugs		
Never vs. Ever exposure	The date of the first dispensation was used to define a time dependent never vs. ever use exposure variable separately for each drug of interest	• Never • Ever

DDD = defined daily doses

9.4.3 Variables Indicating Intensity of COPD Treatment

Intensity of COPD treatment was applied as a possible marker of COPD disease severity. A TIS was derived based on the use of the drugs listed in Table 5 during the 4 months before cohort entry. To determine any changes in treatment intensity, use of medications was also explored in the 4-month time window 9 to 12 months before CE (Table 6) and compared to use in the 4 months immediately before cohort entry.

Table 5 Definition of Use of COPD Drugs With Coding 4 Months Before Cohort Entry Date

Variable	Description	Categories
SAMA use 4 months before CED	Any dispensation of SAMA (ATC codes R03BB01, R03BB02, R03AL01 (GER only) R03AL02 or GPI code 44100030x) in the 4 months before CED	• No • Yes
SABA use 4 months before CED	Any dispensation of SABA (ATC codes R03AC02, R03AC03, R03AC04, R03AK04 (GER only), R03AL01 (GER only) R03AL02, R03CC03 (GER only) or GPI codes 44201010x, 44201045x, 44201050x) in the 4 months before CED	• No • Yes
LAMA use 4 months before CED	Any dispensation of LAMA (ATC codes R03BB04, R03BB05, R03BB06, R03BB07, R03AL03, R03BB54 (GER only), R03AL05 (GER only), R03AL04 or GPI codes 44100007x, 44100080x) in the 4 months before CED	• No • Yes
LABA use 4 months before CED	Any dispensation of LABA (ATC codes R03AC11, R03AC12, R03AC13, R03AC18, R03AK06, R03AK07, R03AK08, R03AK09 (GER only), R03AK10 (GER only), R03AK11, R03AL03, R03AL04, R03AL05 (GER only) or GPI codes 44201012x, 44201027x, 44201042x, 44201058x) in the 4 months before CED	• No • Yes
ICS use 4 months before CED	Any dispensation of ICS (ATC codes R03BA01, R03BA02, R03BA05, R03BA07, R03BA08, R03AK06, R03AK07, R03AK08, R03AK09 (GER only), R03AK10 (GER only), R03AK11 or GPI codes 44400010x, 44400015x, 44400017x, 44400030x, 44400033x, 44400036x, 44400040x) in the 4 months before CED	• No • Yes

ATC = anatomical, therapeutic and chemical; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; GPI = generic product identifier; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist; SWE = Sweden

Intensity of COPD treatment in the 4-month interval from 9 to 12 months before CE (used to evaluate change in treatment intensity) was based on the 5 binary variables shown in Table 6.

Table 6 Definition of Use[a] of COPD Drugs 9 to 12 Months Before CED

Variable	Description	Categories
SAMA use 9 to 12 months before CED	Any dispensation of SAMA 9 to 12 months before CED	• No • Yes
SABA use 9 to 12 months before CED	Any dispensation of SABA 9 to 12 months before CED	• No • Yes
LAMA use 9 to 12 months before CED	Any dispensation of LAMA 9 to 12 months before CED	• No • Yes
LABA use 9 to 12 months before CED	Any dispensation of LABA 9 to 12 months before CED	• No • Yes
ICS use 9 to 12 months before CED	Any dispensation of ICS 9 to 12 months before CED	• No • Yes

[a] Based on new drug dispensations

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist

9.4.4 Propensity Score Variables

The variables shown in Table 7 were used in constructing the PS, for each country as indicated.

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Demographics					
Sex		• Male • Female	X	X	X
Age	Age at CED	NA	X	X	X
Military rank	Proxy for socioeconomic status (SES)	• Officer • Enlisted • Warrant Officer/ Other/NA	-	-	X
SHI contributing data to GePaRD	Proxy for SES	-	X	-	-
History of alcoholism / alcohol abuse	History of alcoholism (ICD-10 codes E24.4, E52 (GER only), F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70.0-K70.4 (K70 in GER), K70.9, K85.20-K85.21, K86.0, O35.4, P04.3, Q86.0, R78.0, T51.0, T51.9, Z50.2, or ICD-9 codes 305.0, 291.xx, 303.xx, 980.xx) and/or use of drugs (ATC codes N07BB01, N07BB03, N07BB04) prior to CED	• History • No history	X	X	X
Obesity	ICD-10-GM E66 or ICD-9 code: 278.00-278.01, 278.03	-	X	X	X
Treatment and comorbidity history					
Type of care in the 12 months before CED SWE	Type of care in the 12 months before CED. Hierarchical approach: 1 Hospitalisation 2 Secondary care 3 COPD medication (including non-chronic antibiotics and non-chronic corticosteroids)	• None • Hospitalisation • Secondary care • COPD medication	-	X	-
Type of care in the 12 months before CED US	Type of care in the 12 months before CED. Hierarchical approach: 1 Hospitalisation 2 Pulmonology outpatient visit 3 Other outpatient visit	• None • Hospitalisation • Pulmonology visit • Other outpatient visit	-	-	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Type of care in the 12 months before CED GER	Type of care in the 12 months before CED (No hierarchy, 3 binary variables): • At least 1 hospitalisation due to COPD • At least 1 visit with any coded EBM at a specialist • at least 1 visit with any coded EBM at GPI	• Yes • No, per variable	X	-	-
Time since diagnosis of COPD/chronic bronchitis at CED	Time (in years) since diagnosis of COPD/chronic bronchitis at CED was approximated as the interval between the first COPD/chronic bronchitis therapy in the prescription records, and CED.	• Under 1 year • 1 to <4 years • 4 to <7 years • 7 to <10 years • ≥10 years		X	
Medication used in the 4 months before cohort entry, based on 5 binary variables	Treatment used in the 4 months before CED: SABA SAMA LABA LAMA ICS	Yes/no for each medication	X	X	X
TIS in the 4 months before cohort entry, based on 5 binary variables	0=no COPD treatment; 1= SABA or SAMA only; 2=LABA or LAMA or ICS (+/- SAMA or SABA); 3=(LABA + LAMA) or (LABA + ICS) or (LAMA + ICS) (+/- SAMA or SABA); 4=LABA + LAMA + ICS (+/- SAMA or SABA);	• TIS = 0 • TIS = 1 • TIS = 2 • TIS = 3 TIS = 4		X	X
Change in treatment intensity over the year before cohort entry	To look at a possible change of severity, the difference was evaluated between intensity of COPD treatment intensity in the 4 months before cohort entry and in the 4-month interval 9 to 12 months before cohort entry.	• Decrease • No changes • Increase 1 • Increase >1 GER: Non-categorised (numeric)	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Number of hospitalisations for any cause in the 12 months before CED	Number of hospitalisations for any cause in the 12 months before CED.	GER: • None • 1 to 2 • ≥3 SWE and US: • None • 1 • 2 or more	X	X	X
Number of hospitalisations due to COPD exacerbations in the 12 months before CED	Number of hospitalisations in the 12 months before CED due to COPD - defined as a main hospital discharge diagnosis ICD-10 code J44 (SWE, GER), or unique inpatient dates with 491, 492, or 496 as the first 3 letters of the primary ICD-9 diagnosis code pertaining to the visit (US).	GER: • None • 1 to 2 • Over 2 SWE and US: • None • 1 to 2 • 3 to 5 • 6 or more	X	X	X
Number of hospitalisations due to COPD exacerbations in the 30 days before CED	Number of hospitalisations in the 30 days before CED due to COPD - defined as a main hospital discharge diagnosis ICD-10 code J44 (SWE, GER), or unique inpatient dates with 491, 492, or 496 as the first 3 letters of the primary ICD-9 diagnosis code pertaining to the visit (US).	• None • Over 0	X	X	X
Number of respiratory disease-related hospitalisations in the 12 months before CED	Number of respiratory disease-related hospitalisations in the 12 months before CED - defined as a main hospital discharge diagnosis ICD-10 code J09-J22, J40-J43, and J45-J47 (SWE, GER), or unique inpatient dates with 460-466, 470-478, 490, 493, 494, 495, 500-508, or 510-529 as the first 3 letters of the primary ICD-9 diagnosis code pertaining to the visit (US).	• None • 1 to 2 • ≥3	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Number of emergency room visits for COPD in the 12 months before CED	Number of emergency room visits in the 12 months before cohort entry due to COPD exacerbation - based on both ICD-10 codes J44 and emergency room codes Emergency Medical Operations, Admission/Emergency Operations, Acute Clinic, Anesthesia and intensive care (SWE), emergency room codes[b] (EBM codes 01210 to 01219, not specified as COPD) (GER), or unique outpatient dates with the primary ICD-9 diagnosis code as 491, 492, 496, and any CPT code on the claim (US). (*Exact codes in Swedish: Jourläkarverksamhet, Intagnings-/Akutverksamhet, Akutklinik, and Anestesi- och intensivvård*)	GER and SWE: • None • Over 0 US: • Yes • No	X	X	X
Number of emergency room visits for COPD in the 30 days before CED	Number of emergency room visits in the 30 days before CED due to COPD exacerbation - based on both ICD-10 codes J44 and emergency room codes Emergency Medical Operations, Admission/Emergency Operations, Acute Clinic, Anesthesia and intensive care (SWE), EBM codes[b] 01210 to 01219 (not specified as COPD) (GER), or unique outpatient dates with the primary ICD-9 diagnosis code as 491, 492, 496, and any CPT code on the claim in US. (*Exact codes in Swedish: Jourläkarverksamhet, Intagnings-/Akutverksamhet, Akutklinik, and Anestesi- och intensivvård*)	GER: • None • 1 to 2 • ≥3 SWE and US: • Yes • No	X	X	X
Number of moderate COPD exacerbations in the 12 months before CED, based on corticosteroids only	Number of dispensations, based on acute use of systemic corticosteroids during the 12 months, not indicating chronic use (ie, not exceeding 8 months' supply) in conjunction with a diagnosis of COPD (US). In GER and SWE, acute use of systemic antibiotics was also included.	• None • 1 to 2 • 3 to 5 • Over 5	X	-	X
Chronic use of systemic corticosteroids in the 12 months before CED	Chronic use of systemic corticosteroids - defined as patients with more than 8-month supply (based on DDDs) of prednisone, prednisolone or betamethasone (ATC codes H02AB06 and H02AB07, or GPI codes 2210x and 2220x) in the 12 months before CED.	• No • Yes	X	-	X
Chronic use of systemic antibiotics in the 12 months before CED	Chronic use of systemic antibiotics - defined as patients with more than 8-month supply (based on DDDs) of systemic antibiotics (ATC codes J01A, J01C, J01DB-DF, J01E, J01FA, J01M, J01R, J01XB01, J01GB01, and J01GB03 or GPI codes 04x, 01x, 0210x, 0220x, 0230x, 0240x, 16000005x, 08x, 16000055x, 03x, 05x, 16000015x, 07000070x, 07000020x) in the 12 months before CED.	• No • Yes	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Status of corticosteroid use in the 12 months before CED	Status of systemic corticosteroid use with 3 levels: acute use of corticosteroids during the 12 months, not indicating chronic use; chronic use (exceeding 8 months' supply); no use (ATC codes H02AB06, and H02AB07 or H02AB01 (SWE only)	• No use • Chronic • Acute	-	X	-
Asthma before CED	Diagnosis (in- or outpatient) of asthma (ICD-10 code J45 or ICD-9 code 493.xx) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Emphysema before CED	Diagnosis (in- or outpatient) of emphysema (ICD-10 code J43 or ICD-9 492.xx) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Current use of theophylline at CED	Current use of theophylline (ATC codes R03DA74 (GER only), R03DA04, or GPI code 430004000x, 44993003301210, 44991002401225, 44991002400130) at cohort entry. All dispensations overlapping CED or ending in the 14-day period before CED.	• No • Yes	X	X	X
Current use of acetylcysteine at CED	Current use of acetylcysteine (ATC code R05CB01 or GPI codes 43300010002003 and 43300010002005) at cohort entry. All dispensations overlapping cohort entry or ending in the 14-day period before CED.	• No • Yes	X	X	X
Charlson Comorbidity Index (CCI)	CCI based on diagnoses any time before CED (US, SWE) or in the 12 months before CED (GER) and as defined in (Quan 2005).	GER: • 0 • 1 to 2 • 3 to 5 • Over 5 SWE and US • 0 to 2 • 3 to 5 • Over 5	X	X	X
Pneumonia and influenza in the 12 months before CED	Diagnosis (in- or outpatient) of pneumonia and influenza (ICD-10 codes J09 - J18 or ICD-9 codes 480.xx-488.xx) in the 12 months before CED.	• No • Yes	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Coronary heart disease, chronic ischaemic heart disease before CED	Diagnosis (in- or outpatient) of coronary heart disease, chronic ischaemic heart disease (ICD-10 codes I20, I24, and I25 or ICD-9 codes 410.xx-414.xx) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Hip fracture in the 12 months before CED	Diagnosis (in- or outpatient) of hip fracture, (ICD-10 codes S72 or ICD-9 codes 820.xx-821.xx or OPS (inpatient) codes 5-790, 5-793, 5-794) in the 12 months before CED.	• No • Yes	X	X	X
Inflammatory bowel disease before CED	Diagnosis (in- or outpatient) of inflammatory bowel disease (ICD-10 codes K50 and K51 or ICD-9 codes 555.xx-556.xx) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Diverticulitis in the 12 months before CED	Diagnosis (in- or outpatient) of diverticulitis (ICD-10 codes K57 or ICD-9 codes 562.11 and 562.13) in the 12 months before CED.	• No • Yes	X	X	X
Osteoporosis in the 12 months before CED	Diagnosis (in- or outpatient) of osteoporosis (ICD-10 codes M80 - M82 or ICD-9 code 733.0x) and/or drug treatment for osteoporosis ATC codes M05BX (SWE only), M05BA, M05BB.	• No • Yes	X	X	X
Annual influenza vaccination in the 12 months before CED	Influenza vaccination (ICD-10 code Z25.1 (SWE only), EBM codes 89111 and 89112 or via CPT and HCPCS codes 90653, 90654, 90655, 90656, 90657, 90660, 90661, 90662, 90672, 90673, 90685, 90686, 90687, 90688, G0008) within 12 months before CED.	• No • Yes	X	X	X
Pneumococcal vaccination before CED	Pneumococcal vaccination (ICD-10 code Z23.8 (SWE only), EBM codes 89118A, 89118B, 89119, 891120, 891120R, or via CPT codes: 90669, 90670, 90732, G0009) within 5 years before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Arterial hypertension before CED	Diagnosis (in- or outpatient) of arterial hypertension (ICD-10 codes I10, I11, I12, I13, and I15 or ICD-9 codes 401.xx-405.xx) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Hyperlipidaemia before CED	Diagnosis (in- or outpatient) of hyperlipidaemia, (ICD-10 code E78 or ICD-9 codes 272.0x-272.4x) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X
Atrial fibrillation (AF) before CED	Diagnosis (in- or outpatient) of AF (ICD-10 codes I48.0, I48.1, I48.2, and I48.9 or ICD-9 code 427.31) any time before CED (US, SWE) or in the 12 months before CED (GER).	• No • Yes	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Deep vein thrombosis (DVT) in the 12 months before CED	Diagnosis (in- or outpatient) of DVT (ICD-10 code I80 or ICD-9 code 453.4x) in the 12 months before CED	• No • Yes	X	X	X
Beta-blockers use 4 months before CED	Dispensation of beta-blockers (ATC codes C07) within 4 months before CED	• No • Yes	X	X	X
Ca-channel blockers use 4 months before CED	Dispensation of Ca-channel blockers (ATC codes C08C, C08D, and C08G) within 4 months before CED	• No • Yes	X	X	X
ACE-inhibitors use 4 months before CED	Dispensation of ACE-inhibitors (ATC codes C09A and C09B) within 4 months before CED	• No • Yes	X	X	X
Angiotensin-receptor blocker use 4 months before CED	Dispensation of Angiotensin-receptor blockers (ATC codes C09C and C09D) within 4 months before CED	• No • Yes	X	X	X
Renin inhibitor use 4 months before CED	Dispensation of renin inhibitors (ATC codes C09XA or GPI code 3617x (Aliskiren) within 4 months before CED	• No • Yes	X	X	X
Diuretic use 4 months before CED	Dispensation of diuretics (ATC codes C03 or GPI code 37x) within 4 months before CED	• No • Yes	X	X	X
Antiarrhythmic drug use 4 months before CED	Dispensation of antiarrhythmic drugs (ATC codes C01B) within 4 months before CED	• No • Yes	X	X	X
Anti-obesity drug use 4 months before CED	Dispensation of anti-obesity drugs (ATC codes A08AB01, A08AA10, and A08AA11) within 4 months before CED	• No • Yes	X	X	-
Statin use 4 months before CED	Dispensation of statins (ATC codes C10AA and C10BA or GPI codes 3940x and 3999x) within 4 months before CED	• No • Yes	X	X	X
Other lipid modifying drug use 4 months before CED	Dispensation of other lipid modifying drugs (ATC codes C10AB, C10AC, C10AD, and C10AX or GPI codes 3900x, 3910x, 3920x, 3930x, 3945x, 3948x, 3950x) within 4 months before CED	• No • Yes	X	X	X
Digitalis use 4 months before CED	Dispensation of digitalis (ATC codes C01AA or GPI code 31200010x) within 4 months before CED	• No • Yes	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Oxygen use 4 months before CED	Dispensation of oxygen (ATC codes V03AN01 or CPT codes: E0424, E0425, E0430, E0431, E0433 - E0435, E0439 - E0444, E1390 - E1392, E1405, E1406, K0738, S8120, S8121) within 4 months before CED	• No • Yes	-	X	X
Antithrombotic drug use (except platelet inhibitors) 4 months before CED	Dispensation of anti-thrombotic drugs (ATC codes B01AA03 (warfarin), B01AA07 (acenocoumarol), B01AA04 (phenprocoumon), B01AX06 (rivaroxaban), or B01AE07 (dabigatran) or B01AF02 (apixaban) (GPI codes 8300x, 8310x, 8320x, 8330x, 8333x, 8337, 8340x) within 4 months before CED	• No • Yes	X	X	X
Platelet inhibitors use 4 months before CED	Dispensation of platelet inhibitors (ATC codes B01AC04, B01AC05, B01AC06, B01AC07, and B01AC22 or GPI code 8515x) within 4 months before CED	• No • Yes	X	X	X
Mood disorder before CED	Diagnosis (in- or outpatient) of mood disorder related to depression (ICD-10 codes F30-F39 or ICD-9 code 296.xx and/or use of antidepressant drugs (SWE only; ATC codes N06A) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X
Psychosis before CED	Diagnosis (in- or outpatient) of mood disorder related to psychosis (ICD-10 codes F20-F29 or ICD-9 295.xx, 290.9x, 298.1x, 298.4x, 298.8x, 298.9x) and/or use of antipsychotic drugs (SWE only; ATC codes N05AA-N05AL, and N05AX) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X
Anxiety disorder in the 12 months before CED	Diagnosis (in- or outpatient) of an anxiety disorder (ICD-10 codes F40-F44 or ICD-9 codes 300.0x, 300.2x, 300.3x, 309.24, 309.28, 309.29, 309.81) within 12 months before CED	• No • Yes	X	X	X
Hyperthyroidism in the 12 months before CED	Diagnosis (in- or outpatient) of hyperthyroidism (ICD-10 codes E05 or ICD-9 codes 242.x) and/or use of anti-thyroid drugs (SWE only; ATC codes H03BA, H03BB, and H03BC) in the 12 months before CED	• No • Yes	X	X	X
Parkinson's disease before CED	Diagnosis (in- or outpatient) of Parkinson's disease (ICD-10 codes G20 or ICD-9 code 332.0) and/or use of antiparkinsonian drugs (SWE only; ATC codes N04) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X

Table 7 Propensity Score Variables

Variable	Description	Categories	GER	SWE	US[a]
Smoking any time before CED[c]	Diagnosis (in- or outpatient) of nicotine dependence, tobacco use NOS (ICD-10 codes Z72.0, F17, Z87.891, Z71.6 or ICD-9 code 305-1x, V15.82) any time before CED	• No • Yes	-	X	X
Multiple sclerosis before CED	Diagnosis (in- or outpatient) of multiple sclerosis (ICD-10 codes G35 or ICD-9 code 340.xx) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X
Lupus erythematosus before CED	Diagnosis (in- or outpatient) of lupus erythematosus (ICD-10 codes M32 or ICD-9 code 710.0x) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X
Cirrhosis before CED	Diagnosis (in- or outpatient) of cirrhosis (ICD-10 codes K74.3, K74.4, K74.5, and K74.6 or ICD-9 code 571.6) any time before CED (US, SWE) or in the 12 months before CED (GER)	• No • Yes	X	X	X
Immunosuppressive medication use 4 months before CED	Dispensation of immunosuppressants (ATC codes L04) within 4 months before CED	• No • Yes	X	X	X
Discharge into rehabilitation/managed care in the 12 months prior to CED[d]	US: Inpatient primary diagnosis of 491, 492, or 496 along with the disposition type: discharged to civilian care, discharged to civilian skilled nursing facility, discharged to civilian intermediate care facility, discharged/transferred to a skilled nursing facility, intermediate care facility, home under care of a home health agency, another rehab facility, nurse facility certified under Medicaid but not Medicare, other institution for outpatient services, this institution for outpatient services GER: EBM codes 01415, 01420, 16231, 40860, 40862, 21231, hospital discharge causes into a rehab facility and into a nursing institution	• No • Yes	X	-	X
Suicidal ideation or action any time before CED	Diagnosis (in- or outpatient) of suicidal ideation or action (ICD-10 codes X71-X83 or Y21-Y33 (SWE only), ICD-10-GM codes X84.9 (GER only) or ICD-9 codes V62.84, E950.xx-E959.xx) any time before CED	• No • Yes	X	X	X
GOLD severity score	Lowest FEV_1 category (5-digit ICD-10-GM code J44) in the 12 months before CED. Patients with unspecific coding or without a 5-digit ICD code were grouped in an extra category. The categories do not match exactly the GOLD-severity categories	-	X	-	-

[a] For all US variables, only ICD-9 codes were used

[b] In GER emergency room codes only indicate emergency care, but it is not known whether this was emergency care in an emergency room at a hospital or emergency care in the outpatient setting (eg, after hours/on the weekend)

[c] Not available in GER

[d] Not available in SWE

ACE = angiotensin converting enzyme; AF = atrial fibrillation; AIDS = acquired immunodeficiency syndrome; ATC = anatomical, therapeutic and chemical; CCI = Charlson Comorbidity Index; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; CPT = current procedural terminology; DDD = defined daily dose; DVT = deep vein thrombosis; EBM = einheitlicher Bewertungsmaßstab (codes for remuneration of outpatient care in Germany); FEV_1 = forced expiratory volume in 1 second; GePaRD = German Pharmacoepdemiological Research Database; GER = Germany; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GPI = generic product identifier; HIV = human immunodeficiency virus; ICD = International Classification of Diseases and Related Health Problems; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; NOS = not otherwise specified; PS = propensity score; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; SES = socioeconomic status; SHI = statutory health insurance; SWE = Sweden; US = United States

Source: Appendix 1 Table 3d; Appendix 2.1 Table 5, 33, 49, 54; Appendix 3.1 Table 5, 51, 56

9.5 Data Sources and Measurement

Patient-level data was obtained from databases in GER, SWE, the US, and NOR as summarised in Table 8.

In GER, data obtained from the GePaRD, built by the Leibniz Institute for Prevention Research and Epidemiology - BIPS in Bremen, was used (Huang and Schink 2021). This database collects medical claims data from 4 German SHI providers (Pigeot and Ahrens 2008) and includes data of more than 25 million insured individuals from all regions in GER since 2004. The database comprises core data, hospital data, outpatient dispensing data, and outpatient medical care data. Information on smoking and other lifestyle related variables is not available in GePaRD. Core data contain information on sex, year of birth, insurance status, and reason for deregistration from the SHI including death. Hospital data comprise the date of admission and discharge, different types of diagnoses including the admission, main discharge, secondary and ancillary diagnoses as well as diagnostic and therapeutic procedures, and the reason for hospital discharge including death. Outpatient medical care data incorporate diagnoses on a quarterly basis with their diagnostic certainty (confirmed, suspected, excluded, and status post), and types and dates of outpatient diagnostic and therapeutic procedures. All diagnoses in GePaRD are coded according to the ICD-10-GM. For simplicity all ICD-10-GM codes that exactly match ICD-10 codes are presented as ICD-10 codes. Where use of a particular code applies to the GER cohort, ICD-10-GM codes are presented. Dispensation data contain information on prescriptions dispensed in a pharmacy and reimbursed by the respective SHI. Drugs purchased over the counter and in-hospital medications are not covered in GePaRD with few exceptions. Dispensation information also includes the dates of the prescription and dispensation, the number of prescribed packages, and the central pharmaceutical number of the drug. Based on a central pharmaceutical reference database, information on the generic and brand name of the drug, packaging size, strength, DDD, and other pharmaceutical information can be linked to GePaRD. Preliminary analyses regarding age and sex distribution, the number of hospital admissions, and drug use have shown that the database is representative for GER and that the insurance population is rather stable over time (Pigeot and Ahrens 2008). Two validation studies of all-cause mortality in GePaRD have been conducted showing acceptable data quality (Ohlmeier 2015, Ohlmeier 2016). Cause-of-death information is not contained in the database. Additionally, linkage of data to a cancer registry was not available in GER. New diagnoses of malignancies were based on claims data only, which presents the limitations described below with respect to the US database.

In SWE, data from the Swedish National Board of Health and Welfare were utilised. These national databases hold data on all inhabitants in SWE and thus cover the complete country population of 9.4 million inhabitants in 2011. The Swedish PDR contains information on prescribed drugs dispensed by community pharmacies from 2005 onwards. According to a quality review of the register, PDR accounts for approximately 80% of total drug utilisation and expenditure in SWE (Wettermark 2007). The Swedish NPR includes all inpatient care in SWE (since 1987) and outpatient visits from 2001 onwards but does not cover primary care yet. Diagnoses recorded in primary care are therefore not captured in the Swedish data and were ascertained by use of proxy drugs. Diagnoses recorded in the NPR have been externally reviewed and are considered highly valid (Ludvigsson 2011). ICD-10 codes indicative of tobacco usage are available in SWE. However, neither smoking status

(currently/former/never), nor smoking intensity/cumulative use (eg, the number of cigarettes/day or packs/year) is recorded. The Swedish Cancer Register is considered to be of good quality mainly because approximately 99% of the cases are morphologically verified. A study in the 1980s showed that the proportion of cases not reported was estimated to be less than 2%, based on information from death certificates (Mattson and Wallgren 1984). The total number of patients in the Swedish Cancer Register (started in 1958) is more than 2 million. A quality study of the Cancer Register was published in 2009 (Barlow 2009)in which the coverage rate was evaluated in comparison to the inpatient registry. In this study, an average underreporting of 4 percent was estimated, but considerable variation exists depending on the cancer site. The Swedish Cause of Death Register provides data since 1953. Data on emigration were available and could be used for censoring, as appropriate.

In the US, data from the MHS since 01 January 2009 were used. MHS is a comprehensive medical network within the US Department of Defense that provides healthcare to all US military personnel, their dependents, and retirees. MHS exclusively covers military service members and their families and has one of the largest health systems in the US, with nearly 10 million patients. Patients enrolled in the MHS receive benefits through the TRICARE nationwide managed care program, which combines healthcare claims from the US Department of Defense facilities with those from the private sector. The MHS is not linked with data streams from the VHA, as the MHS and the VHA are separate entities; therefore, this study does not contain data from the VHA patient population. MHS data contain records on all healthcare events (that are required to be reported) paid for by the MHS, regardless of setting. Patients are insured through MHS; however, they are not required to use military medical facilities. Many patients use their MHS coverage to obtain care in civilian facilities. The MHS contains robust historical beneficiary data, including coverage information, service-related information and demographics, and clinical data (eg, vital signs, body mass index).

Diagnostic coding is based on ICD-9 codes through October 2015 and ICD-10 codes thereafter (thus, ICD-9 codes were used for PS variables in this study). Information on procedures is available through codes of the Healthcare Common Procedures Coding System, including current procedural terminology codes. Information on drug dispensations is available as NDC (GPI and ATC codes were mapped to NDC for this study). ICD-9 codes indicative of tobacco usage are available in the database. However, neither smoking status (currently/former/never), nor intensity/cumulative use (eg, the number of cigarettes/days or packs/years) is recorded. The MHS contains a death code and the date of death. Death data in the MHS comes from the following sources: deaths in military facilities (available near real-time), deaths within civilian facilities (available near real-time), combat-related deaths (available near real-time, though, irrelevant in this study), survivor self-report directly to TRICARE, and a contracted, recurring Social Security Death Index feed from the Social Security Administration. All death data are processed and direct-linked to the beneficiary within a master death file. The lag in death reporting is minimal for deaths at military facilities (average 30 to 60 days), while deaths within civilian facilities are captured in the data within approximately 60 to 90 days. Remaining deaths occurring outside of a bedded facility (ie, from survivor self-report and/or the Social Security Death Index data) are captured within approximately 4 to 6 months.

The MHS data has been used by many research teams to examine all-cause mortality as well as specific causes of death, when linked to the US National Death Index (Andaya 2013, Capkun 2015, Lin 2016, Lin 2017, Manjelievskaia 2017, Meyers 2008, Nee 2017, Schoenfeld 2017, Zheng 2012, Zogg 2016). Cause of death is not available for this study, as the MHS data was not linked to the National Death Index. Furthermore, no linkage to a cancer registry was available in the US study, which resulted in the identification of new diagnoses of malignancies from the claims data only. The limitations of this setting for the study of cancer incidence include the lack of morphological confirmation of the diagnosis, limited staging information, and limited baseline observation period often insufficient to distinguish prevalent and incident cancer cases.

In Norway, data from the national Norwegian registries were used. The registries are held by different authorities that managed the data extractions and data linkage. The National Population Register is held by the Tax Administration, the NPR-Nor is held by the Norwegian Directorate of Health, the Cancer Registry of Norway is held by the Oslo University Hospital Trust, the Norwegian Cause of Death Registry and the NorPD are both held by the Norwegian Institute of Public Health. These national registries hold data on all inhabitants in Norway and thus cover the complete population of 5.3 million inhabitants. NorPD contains information on drugs dispensed by prescription from 2004 onwards. The NPR-Nor registry includes all inpatient and outpatient, public and private, specialist healthcare from 2008 onwards. NPR-Nor data has been shown to have a high degree of completeness (Bakken 2019). The Cancer Registry of Norway contains data from 1952 onwards and has relative high validity compared to other European registries (Larsen 2009). Primary care diagnoses are not captured in these registries and were ascertained by drug proxies. The Cause of Death Registry provides data from 1951 onwards.

Table 8 Registers and Their Primary Use in the Study

Country	Register	Register/database Holder	Type of Data
GER	German Pharmacoepdemiological Research Database	Leibniz Institute for Prevention Research and Epidemiology-BIPS	Core data (demographics), hospital data, outpatient care data, outpatient drug dispensations data
SWE	Swedish Prescribed Drug Register	Swedish National Board of Health and Welfare	Dispensed drugs in community pharmacies
SWE	National Patient Register	Swedish National Board of Health and Welfare	Inpatient discharge and outpatient care discharge diagnoses[a]
SWE	Swedish Cause of Death Register	Swedish National Board of Health and Welfare	Date and cause of death
SWE	Swedish Cancer Registry	Swedish National Board of Health and Welfare	Cancer diagnoses
US	Military Health System	Department of Defence	Core data, hospital data, drug dispensed in pharmacy, and claims data
NOR	National Population Register	Tax Administration	Demographics
NOR	NPR-Nor	Norwegian Directorate of Health	Inpatient and outpatient, public and private, specialist healthcare
NOR	Cancer Registry of Norway	Oslo University Hospital Trust	Cancer diagnoses
NOR	Norwegian Cause of Death Registry	Norwegian Institute of Public Health	Date and cause of death
NOR	NorPD	Norwegian Institute of Public Health	Drugs dispensed by prescription

[a] National Patient Register includes all inpatient care in Sweden (since 1987) and outpatient visits from 2001 but does not cover primary care yet. Diagnoses recorded in primary care were therefore ascertained by use of proxy drugs.

GER = Germany; NOR = Norway; NorPD = Norwegian Prescription Database; NPR = Norwegian Patient Register; SWE = Sweden; US = United States

9.6 Bias

9.6.1 Confounding

Confounding by indication/COPD severity is of high concern, since a cohort exposed to a drug indicated for severe COPD, on top of previous treatments in a patient segment where no alternative treatment is available, is compared to an unexposed cohort and not compared to an active comparator drug indicated for similar high COPD severity, thus leading to higher disease severity in the roflumilast exposed cohort. PS matching of exposed and unexposed cohorts (as detailed in Section 9.3.7) aimed to form cohorts with similar baseline characteristics and comparable markers of COPD disease severity, which are supposed to be related to factors that may have influenced the administration of treatment (Austin 2011). In the ideal situation, where all relevant baseline characteristics are measured without error and taken into account directly in the matching algorithm, all sources for confounding are balanced out. The independent variables included in the PS model are factors that have been associated with roflumilast treatment (ie, COPD severity) and the study outcomes of interest.

For example, patients with a diagnosis of asthma as well as COPD or chronic bronchitis are not excluded from the analyses, but since such patients may have a higher likelihood of exposure to roflumilast and also a higher mortality risk, asthma as a comorbidity was included in the PS model. Of note, time since diagnosis of COPD/chronic bronchitis at CED was used in the PS model in SWE but not in the GER or US models.

Cox proportional hazard regression models that included covariates that were imbalanced after PS matching were used to obtain adjusted HRs for the analyses of primary and secondary outcomes.

The PS-matching attempted to make exposed and unexposed cohorts comparable at baseline (ie, at CED) by generally assessing data within 1 year before CED. However, analyses at CED-1 in all countries and also at CED-2 in SWE indicated that the exposed cohort included more patients with a higher degree of severe COPD than the unexposed cohort. Furthermore, given the imperfect balance at cohort entry, the distribution of time-dependent determinants for treatment assignment and study outcomes is likely to change differentially over time in exposed and unexposed patients. To verify this assumption, the distribution of the variables related to COPD severity which were included in the PS score in exposed and unexposed cohorts was not only assessed at CED (baseline), but also at years 1 to 5 of follow-up, ie, at years CED+1, CED+2, CED+3, CED+4, and CED+5, where available.

Smoking is an important risk factor for the primary and selected secondary outcomes (among others, new malignancies) and it may also be related to roflumilast exposure since smoking increases the risk of COPD exacerbations which are a major reason to prescribe roflumilast. ICD-9 codes and ICD-10 codes indicative of current or former tobacco use in the US and SWE respectively, were included in the PS. However, due to the low quality and incompleteness of these data, smoking should be considered as a potential unmeasured confounder, despite a proxy for it being included in the PS model. For instance, in SWE coding for current or former tobacco use was identified in only approximately 13.3% of the exposed patients and 12.7% of the unexposed patients, whereas it is well known that the majority of COPD patients are current or former smokers. Furthermore, timing, duration and quantity of tobacco consumption remained unmeasured.

9.6.2 Selection Bias

A possible risk for selection bias was hypothesised for “last resort prescribing” of roflumilast to very ill patients with a high risk of dying in the near future. Such prescribing would identify exposed patients shortly before death, with no chance for roflumilast to change the prognosis. To minimise the risk of this bias, sensitivity analyses were performed in the second and third interim reports and repeated in this final report, which excluded all patients who died within i) 3 and ii) 12 months after the CED. The short period of 3 months was selected because of the high number of patients with only 1 dispensation.

Since the study included all roflumilast-exposed patients directly after launch of the drug in GER, SWE, and the US, selection bias could arise if patients treated with roflumilast in the first months after launch differed from those treated later due to a “new drug effect.” To mitigate this potential bias, PS models were calculated for each month of each CE year, which should limit channelling, as the matching would naturally account for the change over time in

prognostic factors that lead to roflumilast prescribing. Furthermore, this potential selection bias was addressed in the second and third interim report and repeated in this final report (SWE and US), with an analysis of the primary outcome that excluded patients who started roflumilast treatment in the first 6 months after launch in the respective countries.

Another important type of selection bias was that patients with exacerbation or more severe disease probably self-select out of the unexposed cohort as they are censored once they start roflumilast. Thus, over time, the patients in the unexposed group would appear to become healthier while those in the exposed group become unhealthier.

Additionally, selection bias could arise if roflumilast was being prescribed to patients with an on average higher risk of mortality than that in the control group, in a way that was not reflected in the elements of the PS. To minimise this potential bias, age, sex, and years since diagnosis of COPD (only available in SWE) were included in the PS matching model.

Finally, the introduction of bias by unknown factors cannot be ruled out in any observational study like this one, based on the use of secondary data collected for purposes other than the research objectives of the study.

9.6.3 Information (Misclassification) Bias

This study utilised claims data to evaluate drug exposure periods; however, whether the dispensed drug had been used could not be ascertained. Drug use periods were constructed based on the number of dispensed DDDs, which could lead to misclassification of exposure in various exposure categories. For example, deviation from the expected treatment regimen or lack of adherence to the prescribed treatment could lead to apparent treatment gaps in exposure, which do not necessarily coincide with treatment discontinuation. To address this bias, the exposure period was prospectively extended by up to 50% of the amount of the previous dispensation in cases where there was no dispensation of roflumilast covering the day after the calculated end of the supply. This also applied to the last roflumilast prescription, since handling the last prescription differently could also lead to bias (Nielsen 2008). Sensitivity analyses were conducted extending the exposure period by 100% or 0% of the amount of the previous roflumilast prescription (as described in Section 9.9.4).

9.7 Study size

The study size per country is described in detail in Section 10.1, with a combined population of 126384 COPD patients (21615 exposed and 104711 unexposed) in the annual cohorts 2011-2013. The power calculations presented in the study protocol were made to ensure sufficient study power for the primary outcome in each country. Power calculations were updated in SWE based on the 2011 cohort to reflect the higher observed MR, but also the higher discontinuation rate of patients with roflumilast treatment.

For 5-year all-cause mortality, the power calculations (Table 9) assuming an increase in the 5-year mortality risk from 40% to 44% (same absolute percent increase as used in the study protocol) provided an 87% or 78% power in the case that 50% or 60% of the roflumilast-exposed patients discontinued use, respectively, and were excluded from the analysis together with their matched unexposed controls.

Table 9 Power Calculation for the Assumption of 50% and 60% Discontinuation During 5-Year Follow-up Per Country

Number of patients exposed	Number of patients unexposed	5-year death rate, exposed	5-year death rate, unexposed	5-year discontinuation rate	Power
3250	16,250	44%	40%	50%	87%
3250	16,250	44%	40%	60%	78%

9.8 Data Transformation

Anonymous patient-level data was transformed to create the demographic, exposure, comorbidity, and outcome variables necessary for analyses. Where applicable, variables were transformed to ordinal (eg, intensity of COPD treatment), categorical (eg, sex), or binary (eg, obesity).

9.8.1 Drug Exposure Data

The total amount of drug dispensed was defined as the number of DDDs or as actual amount (in µg) dispensed. The number of DDD provides a measure of how long the intake of a drug would last if taken as 1 DDD per day. Based on the dispensing data, namely number of DDD and package size, each dispensation was translated into a drug exposure period. The assumptions described in Section 9.4.2 enabled concatenation of consecutive dispensations into a continuous drug exposure period, therefore permitting exposure status definition as current, recent, and past. These assumptions were also used to define time since discontinuation.

Cumulative dosage throughout follow-up was established based on the total DDDs dispensed.

9.9 Statistical Methods

The planned statistical methods are detailed in the Core SAP. Country-specific differences in the analyses are described in the GER, NOR, SWE, and the US SAP adaptations. The statistical methods are described briefly below.

9.9.1 Main Summary Measures

For the matched exposed and unexposed cohort, the distribution of the cohort matching variables (listed in Section 9.3.7) and PS variables (Table 7) are presented for the 2011, 2012, and 2013 annual cohorts separately and for the pooled 2011-2013 annual cohorts per country. The characteristics of the annual study cohorts were assessed during the baseline year prior to CED.

Summary measures of the matching variables and other study variables were compared between exposed and unexposed patients in each study year before and after matching. For unexposed patients, the summary measures prior to matching were evaluated at the first of January of each study year (SWE and US) or the first potential matching date, ie, the fifteenth of the month when the inclusion criteria were first fulfilled (GER).

Categorical variables are described as counts and percentages while continuous variables are described with measures of central tendency and dispersion (min/max, median, mean, and SD). Where applicable (eg, demographic data), p-values were calculated using the Fisher's exact test for categorical variables and t-test for continuous variables. The 95% CI were calculated for key parameters including, but not limited to, crude IR and IRR, crude MR and MRR. The 95% CI were computed using the substitution method (Daly 1998), which assumes that the number of events was Poisson-distributed and the person-time fixed and without sampling variation. Percentages, rates, ratios, means, medians, quartiles, and CIs are reported to 2 decimal places, and days are rounded to full days where applicable. The median and interquartile range were used to describe the time spent in the cohort for exposed and unexposed patients, from CE until death or censoring. The percentage of patients with repeating events was calculated for each possibly repeating event. The mean, median, first quartile, third quartile, and range of these possibly repeating events were also reported along with the number of patients experiencing an event and the number of events experienced per patient.

9.9.2 Main Statistical Methods

9.9.2.1 Matching

The matching between exposed and unexposed patients was performed at baseline by sex, age (±1 year), calendar year of cohort entry, PS, and time since diagnosis (SWE only).

9.9.2.2 Propensity Score

Conventional Propensity Score

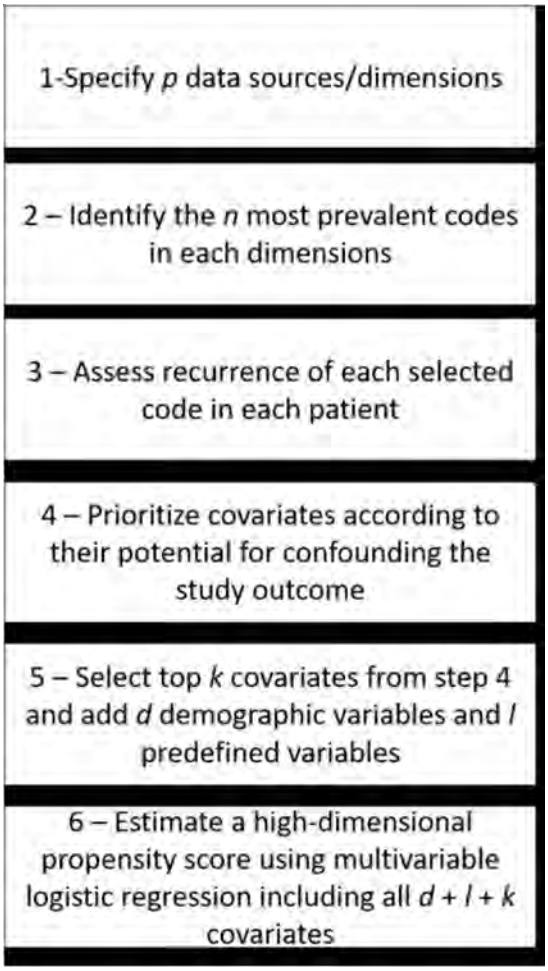
A tailored monthly PS model was developed. The PS estimated the likelihood among COPD patients of receiving roflumilast at each potential CED versus not receiving roflumilast. The exposed patients had only one possible CED; all CEDs of the exposed patients were potential CEDs for the unexposed patients.

The goal was to estimate the PS for all unexposed at all potential CEDs. This task was simplified by estimating the PS on a monthly grid (at the 12 potential time points per year). At each time point a separate PS model was fitted using the PS variables evaluated at the fixed CEDs for the exposed and the PS variables evaluated at the grid point for the unexposed patients. When matching for an exposed patient with a CED in a given month, the control patient's PS was their PS for the PS model for the exposed patient's CED month. The PS variables are listed in Table 7.

High-dimensional Propensity Score

A HDPS was developed as a sensitivity analysis for the primary outcome using a multi-step algorithm summarised in Figure 1 and detailed in the Core SAP Section 6.3. The HDPS aimed to empirically identify candidate covariates which may collectively be proxies for unobserved confounding of the outcome. The algorithm intakes a large number of possible confounding covariates extracted from longitudinal health data. It first removes covariates with low prevalence and then removes covariates with a low potential for causing bias. The resulting selected covariates are then entered in a conventional PS model.

Figure 1 High-dimensional Propensity Score Methodology



Source: Core SAP, Figure 1

9.9.2.3 Method of Matching

The distribution of the PS was examined between exposed and eligible unexposed matches. For PS matching to work well, there must have been a sufficient overlap in the distribution of the PS between the 2 groups. The aim was to have 5 unexposed matches for each exposed patient. A patient could only be selected as an unexposed match once in this study. However, an unexposed match could re-enter the study as a roflumilast exposed patient in the consecutive annual cohorts.

9.9.2.4 Criterion for Propensity Score Matching

Matching was stratified by sex, age (±1 year), calendar year of cohort entry, and PS. From the PS model, the logit to the PS was used. The width of the matching interval (Δ) was derived as 0.2 times the SD of the logit to the PS. A common width of the matching was used for the 2011-2013 cohorts. With a maximum of 5, as many unexposed patients meeting the matching criteria as possible were selected for each exposed patient.

Matching was done in 5 separate rounds in SWE and the US (sequential scheme), whereas in GER up to 5 unexposed controls were matched simultaneously to each exposed patient (parallel scheme [Rassen 2012]).

In the sequential scheme, within each round the selection of the matches was done in a random order of the exposed cohort. In each round if there were multiple potential matches available for an exposed patient, then the potential matches were sorted by (ascending) absolute difference in the logit PS, and the match on the top of this list was selected. In case of a tie the choice was made randomly.

For the parallel scheme, matching was done for each annual cohort, and in the sequential scheme, matching was done simultaneously for all extracted cohorts so that in each round a match was selected in a random order for all exposed patients irrespective of the year of cohort entry.

Exposed patients without matched unexposed patients are described separately.

9.9.2.5 Standardised Difference

Since the number of unexposed to exposed is the same for the vast majority of patients (5:1 for >93%), standardised differences for the variables included in the calculation of the PS were calculated using the normal unweighted formula provided (Austin 2008). The success of the matching procedure was measured based on the standard difference of each covariate with values less than 0.1 between treatment groups indicating negligible difference, a cut-off value that has been applied before (Austin 2011). Standardised differences for proportions were calculated using the following formula:

$$d = \frac{|p_1 - p_2|}{\sqrt{\frac{p_1(1-p_1) + p_2(1-p_2)}{2}}}$$

where p_1 and p_2 denote the prevalence in exposed and unexposed patients, respectively.

For a continuous variable the formula is:

$$d = \frac{|\overline{x_1} - \overline{x_2}|}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

where $\overline{x_1}$ and $\overline{x_2}$ denote the sample means; s_1^2 and s_2^2 sample variances in exposed and unexposed patients, respectively.

Balance analyses on the distribution of PS variables among treated and untreated patients, with respect to the standard difference of each covariate of 0.1 or above between treatment

groups were performed at CED in all countries. Additionally, in all countries the balance analysis was repeated for the entire country cohort at CED-2, CED-1, CED+1 to CED+5 years.

9.9.2.6 Analyses of the Primary, Secondary, and Exploratory Outcomes

The MRs for the primary outcome and IRs for secondary outcomes are reported. The MRR for the primary outcome and the IRRs for the secondary outcomes were calculated by dividing the MR (or IR) for different roflumilast exposure categories by the rate in those never exposed to roflumilast.

The IRs with 95% CIs were calculated for all exposure definitions of roflumilast for all secondary endpoints except for the secondary endpoint "new diagnosis of malignant neoplasm" where ever use of roflumilast was considered the relevant exposure.

Cox proportional hazard regression modelling was applied to estimate crude and adjusted HRs with the aim to account for unbalanced PS variables and other known determinants of the study outcomes. Since balance by PS matching could not be assumed, balance analysis at baseline was conducted for important markers of COPD severity or risk factors for the study outcomes using standardised differences. In the adjusted Cox proportional hazard analyses, age, sex, and covariates for which the standardised difference was >0.1 between the exposed and unexposed groups after PS matching were included as covariates. Although matched for the categorical variables sex and age, these variables were also included in the Cox model, since the balance at CE may change during follow-up due to non-random censoring (eg, a previously unexposed patient becoming exposed to roflumilast). The annual matched set was combined into 5 strata according to quintiles of the PS distribution of the exposed patients in each year. The resulting 15 strata (5 strata per CE year) were used as strata in the Cox model. In the analyses on the primary outcome, variables related to COPD severity and general morbidity (Table 10) were also included in the Cox model for additional adjustment.

Table 10 Variables as Markers of COPD Severity and Healthcare Utilisations and General Health

Variable	GER	SWE	US
COPD severity and general morbidity			
Number of hospitalisations due to COPD exacerbations in the 12 months prior to CED:0/1-2/>2 (GER) and 0, 1-2, 3-5, ≥6 (SWE, US)	X	X	X
Hospitalisation due to COPD exacerbation in the 30 days before CED: 0, ≥0	X	X	X
Number of respiratory disease-related hospitalisations in the 12 months before CED: 0, 1-2, ≥3	X	X	X
Number of emergency room visits for COPD in the year before CED: 0, 1, ≥2	X[a]	X	X
Emergency room visit for COPD in the 30 days before CED: 0, ≥0	X[a]	X	X
Prior use of oxygen: Yes/No	--	X	X
Current use of theophylline or acetylcysteine at CED: Yes/No	X	X	X
Charlson Comorbidity Index any time before CED: 0, 1-2, 3-5, >5 (GER); 0-2, 3-5, ≥6 (SWE, US)	X	X	X
Emphysema: Yes/No	X	X	X

Table 10 Variables as Markers of COPD Severity and Healthcare Utilisations and General Health

Variable	GER	SWE	US
COPD severity and general morbidity			
Number of moderate COPD exacerbations in the 12 months before CED: 0, 1-2, 3-5, >5	X	X	X
Treatment intensity score: 0, 1-2, 3, 4	X	X	X
Chronic use of systemic corticosteroids Yes/No	X	X	X
Number of COPD-related physician visits in the 30 days before CED	X	X	X

[a] In GER, emergency room codes only indicate emergency care, but it is not known whether this was emergency care in an emergency room at a hospital or emergency care in the outpatient setting.

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; SWE = Sweden, US = United States

Since full balance for risk factors of secondary outcomes might not have been achieved by PS matching as was already discussed for the primary outcome, disease specific adjustment variables for each secondary outcome were defined based on medical knowledge (referred to as Model 4). These adjustment variables represented either risk factors for the respective secondary outcome or measures of healthcare utilisation presumed by the investigator team to be related to disease severity. These additional covariates were not used in the SWE analysis.

With regard to 5-year all-cause mortality, the formal statistical hypotheses between any 2 treatment groups (ever versus never exposed) was as follows:

$$H_0 : HR = Mortality_{roflumilast} / Mortality_{REF} = 1$$

Against the alternative

$$H_1 : HR = Mortality_{roflumilast} / Mortality_{REF} \neq 1$$

Where HR denotes the hazard ratio, $Mortality_{roflumilast}$ denotes the 5-year all-cause mortality risk in the group of COPD patients ever exposed to roflumilast, and $Mortality_{REF}$ denotes the 5-year all-cause mortality risk in the reference group of COPD patients never exposed to roflumilast. For other study endpoints and other roflumilast exposure definitions, similar hypotheses were applied.

In the calculation of the crude IRs of malignant neoplasms, persons with a history of cancer were excluded from the analysis. Additionally, a latency period of 1 year or 2 years was accounted for in the analysis of malignant neoplasms by moving the start of follow-up by 1 or 2 years, thus excluding both follow-up time and events during the latency period for all patients.

In the calculation of the crude IRs of new depression, persons with a diagnosis of depression before CED were excluded from the analysis. A previous diagnosis of depression was also checked for switchers from the unexposed to the exposed cohort.

Similarly, for the endpoint concerning new diagnoses of tuberculosis or of hepatitis B or C or other severe viral hepatitis (except hepatitis A), individuals who had these diseases before CED were excluded from the analyses. Due to exclusion of patients with prior disease, numbers of patients are different in these analyses from those in the full cohort.

The primary and secondary outcomes were evaluated by Cox proportional hazards regression models for counting processes, which allowed follow-up time to be divided into several periods and thus control for baseline and time-dependent covariables, using the full observational period of available data.

9.9.3 Missing Values

If a variable was 100% missing from a database (eg, FEV_1 in the US and SWE), it was excluded from the analysis. If a variable was only partially available (eg, FEV_1 usually only for hospitalised patients in GER), a missing category for those patients for whom no information on that variable was available was formed. If information on a particular variable was available in a data source, patients were assumed not to have the factor if there was no evidence for its presence (eg, if a variable indicating a disease was not coded for a patient in a database, the patient was assumed not to have the disease).

9.9.4 Proportional Hazards Assumption Test

The assumption of proportional hazards was evaluated for each outcome by plotting the smoothed Schoenfeld residuals against survival times for each exposure time-independent variable (Grambsch and Therneau 1994).

9.9.5 Sensitivity and Exploratory Analyses

The following sensitivity and exploratory analyses were performed in the second and third interim reports and repeated in this final analysis:

9.9.5.1 Sensitivity analyses:

- A sensitivity analysis of 5-year all-cause mortality similar to the primary analysis was conducted by excluding mortality events (and associated person-time) in the first 3 and 12 months after CED, respectively. This was intended to exclude possible bias introduced by severely ill COPD patients in whom roflumilast might have been used as a "last resort." The short period of 3 months was selected because of the large number of patients with only 1 roflumilast dispensing.
- The definition of current, recent, and past use of roflumilast includes a gap extension assumption (see Section 9.4.2). In the adjusted Cox regression analyses of 5-year all-cause mortality, sensitivity analyses were conducted in the US and SWE to test the robustness of the gap extension definition, by changing the gap extension from 50% to 100% or 0% of the amount of the respective prior dispensed roflumilast prescription. These sensitivity analyses applied to current, recent, and past use of roflumilast.
- Sensitivity analysis with respect to early discontinuation. In this sensitivity analysis patients were required to have at least 2 prescriptions/dispensations within 6 months (180 days) from CED in order to be included in the study as ever exposed (SWE and US).

- Sensitivity analysis with respect to initiation of treatment soon after product launch. Selection bias may occur if patients who receive roflumilast within 6 months from initial launch are significantly different from those who initiate the product after 6 months of launch (early adopter bias). In this sensitivity analysis patients who initiated roflumilast treatment within 6 months after launch were excluded. The unexposed matches of the excluded exposed patients were also excluded (SWE and US).
- Sensitivity analysis with respect to age. The MR is highly dependent on age. In this sensitivity analysis patients with age over 80 at CED were excluded (SWE and US).
- The effect of number of roflumilast dispensations was addressed in an analysis employing an alternative cumulative dose analysis. Roflumilast exposure was based on the number of dispensations. This time-dependent exposure variable was categorised as follows: "0," "1," "2-3," "4-9" and ">10."
- A stratified analysis of the primary outcome (5-year all-cause mortality) was conducted by FEV_1 values according to the categories presented below. In the GER data, for approximately 70% of all matched patients (mainly in-hospital patients), specific FEV_1 values were captured in the German coding system by the fifth digit ICD-10-GM J44 as follows:
  - 0 = FEV_1 <35 %,
  - 1 = FEV_1 ≥35 % and <50 %,
  - 2 = FEV_1 ≥50 % and <70 %,
  - 3 = FEV_1 ≥70 %
  - 9 = not further specified
- Sensitivity analyses for hospitalisation for suicide attempt, using (i) only X84.9! ("intentional self-harm") and (ii) only code X84.9! but also considering inpatient secondary diagnoses, were performed. (GER only, since code X84.9! is not available in SWE or the US).
- A sensitivity analysis was conducted for the main 5-year all-cause fatality using an HDPS approach. In this analysis, a HDPS was developed and used for matching exposed to controls.

9.9.5.2 Exploratory Analyses

- Mortality risk calculated in quintiles of the PS: Propensity scores of the accumulated annual cohorts were categorised using quintiles. Instead of adding the PS as strata to the model, the adjusted HR for 5-year all-cause mortality with 95% CI was calculated separately within each quintile for the roflumilast ever exposed versus never exposed.
- Asthma subgroup analysis: The effect of asthma was investigated in subgroup analyses among patients with and without asthma at CED. After creating each of these 2 subgroups based on the asthma status, matched strata without at least one exposed and unexposed were completely removed.

9.9.5.3 Additional sensitivity and exploratory analyses

In addition to the analyses listed above, the following additional sensitivity and exploratory analyses were included in the third interim report and repeated in this final report:

Sensitivity analysis:

- ITT sensitivity analysis for 5-year all-cause mortality to address the influence of patients who switched from the unexposed group to the exposed group. In this design switchers from the unexposed group remained unexposed upon roflumilast initiation until the end of study, disenrollment from the database (migration or other reason) or death. They were not analysed in the exposed group and their unexposed controls were excluded from the analysis.

Exploratory analyses:

- Further adjustment of the Cox model with unbalanced covariates at CED-1. Unbalanced covariates were defined as having a standardised mean difference above 0.1 and were included as covariates in the model (SWE and US).
- To investigate long-term cumulative exposure, an analysis for 5-year all-cause mortality was conducted where cumulative exposure duration was subdivided into <3 months, 3 to 12 months, >12 to 24 months, and >24 months. Cumulative exposure was also categorised as ≤12 months, >12 to 24 months, and >24 months and evaluated in association with current, recent, and past use of roflumilast.
- Additional analyses related to recent use to further investigate the observed increased risk of death in the recent use period: for patients who died during the recent use period, the number of patients with at least 1 hospitalisation for respiratory disease and at least 1 hospitalisation for any cause were calculated in 3 time intervals, namely during recent use, 0 to 55 days and 56 to 110 days before the recent use period.
- Analysis for 5-year all-cause mortality according to each year of follow-up time within a single model.

In addition to the above analyses specified in the SAP, an analysis was conducted to describe the distribution of exposed and unexposed patients in the 5 PS quintiles by FEV_1 strata in the GER data (information on FEV_1 was only available in the GER database). This analysis presented in Table 56 complemented the stratified analysis of the primary outcome (5-year all-cause mortality) by FEV_1 values.

9.9.6 Meta-analysis

A meta-analysis was added as a planned analysis for this final report following PRAC advice provided following review of the third interim report. The aim of the meta-analysis was to pool model estimates obtained from each of the countries for the main analysis of primary and selected secondary outcomes as well as for the HDPS sensitivity analysis of the primary outcome. The planned analyses are detailed in the Combined Country Meta – Analysis SAP (version 2.0, dated 31 March 2022) and described briefly below.

9.9.6.1 Endpoints of Meta-analysis

The meta-analysis included analysis of the primary endpoint of 5-year all-cause mortality and the following secondary outcomes:

- All-cause mortality
- Hospitalisation for any cause
- Major cardiovascular events leading to hospitalisation, composite of:
  - Arrhythmia (conduction disorders and dysrhythmias)
  - Myocardial infarction
  - Cerebral infarction or stroke not specified as haemorrhage or infarction
  - Heart failure
  - Pulmonary embolism,
- Respiratory disease-related hospitalisation,
- New diagnosis of malignant neoplasm (except nonmelanoma skin cancer).

9.9.6.2 Meta-analysis Methodology

Log-transformed HRs and their standard errors were entered into a random-effects meta-analysis model. Meta-analysis models used the generic inverse-variance method. For the random-effects analysis, the amount of residual heterogeneity was estimated using the DerSimonian-Laird estimator.

Heterogeneity between the study countries was estimated using Higgins' and Thompson's I^2 and the moment-based estimate of τ^2. Both I^2 and τ^2 were derived using Cochran's Q statistic defined as:

$$Q = \sum_{k=1}^{K} w_k \left(\hat{\theta}_k - \frac{\sum_{k=1}^{K} w_k \hat{\theta}_k}{\sum_{k=1}^{K} w_k} \right)^2;$$

where $\hat{\theta}_k$ denotes the logHR, $\hat{\sigma}_k$ denotes its standard error, K denotes the number of studies in the meta-analysis, and $w_k = \frac{1}{\hat{\sigma}_k^2}$ denotes the corresponding weight from the study k.

I^2 Statistic

I^2 is the percentage of variability in the treatment estimates which is attributable to heterogeneity between studies rather than to sampling error. I^2 is sensitive to the precision of the included studies, with higher I^2 associated with increased precision in individual studies. I^2 is given by:

$$I^2 = \max\left\{0,\ Q - \frac{K-1}{Q}\right\};$$

where K is the number of the studies included and Q is Cochran's Q statistic.

τ^2 Statistic

The τ^2 Statistic is insensitive to the number of studies or to their precision but can be difficult to interpret. The DerSimonian and Laird estimate will be computed using the formula below:

$$\hat{\tau}^2 = max\left\{0, \quad \frac{Q-(K-1)}{\sum_{k=1}^{K} w_k - \frac{\sum_{k=1}^{K} w_k^2}{\sum_{k=1}^{K} w_k}}\right\}$$

where K is the number of the studies included, Q is Cochran's Q statistic and $w_k = \frac{1}{\hat{\sigma}_k^2}$ denotes the corresponding weight from the study k.

The main analysis results were reported using forest plots.

9.9.6.3 Sensitivity Analysis

The meta-analysis was conducted using GER, SWE, and US data since NOR data were not available at the time of this report. Given the small sample size for NOR, the planned meta-analysis including NOR will not be conducted.

9.9.7 Amendments to the Core Statistical Analysis Plan

The core SAP was amended 5 times in total. Modifications made with each of these amendments are summarized below and further specified in Appendix 6 of the Core SAP.

9.9.7.1 Amendment 5 of the Core Statistical Analysis Plan

Date: 11 February 2022

The following changes to the previous analyses were made:

- The Ever/Never exposure was removed for the analysis of the individual active events that make up the composite major cardiovascular event outcome. This decision was made on the grounds that the Ever/Never exposure definition is not relevant for acute events.
- Weighted Schoenfeld residuals were produced only for **exposure** time-independent covariates (versus all time-independent covariates). The rationale was that if the proportional hazard assumption was not met for a non-exposure covariate, it would not affect the estimation of the exposure related hazard-ratio, which is the estimate of interest in this study.

9.9.7.2 Amendment 4 of the Core Statistical Analysis Plan

Date: 02 October 2020

The following changes to the previous analyses were made:

- Specified that data was to be extracted from Norwegian national healthcare registries. These registries are the National Population Register, the Norwegian patient register, the Cancer Registry of Norway, the Norwegian Cause of Death registry and the NorPD.
- In addition to random matching with a matching calliper width of 0.2 times the SD of the logit of the PS, the effect of (1) balanced matching and (2) reducing the matching calliper width to 0.1 times the SD of the logit of the PS on the post-matching balance of variables of interest was to be investigated. An alternative matching method was to be adopted if it provided an obvious improvement in this balance.
- An additional sensitivity analysis was to be conducted for the main 5-year all-cause fatality using an HDPS approach. In this analysis, an HDPS was developed and used for matching exposed to controls as specified in Section 9.4.2.3 of the Core SAP.

9.9.7.3 Amendment 3 of the Core Statistical Analysis Plan

Date: 12 December 2018

The following changes to the previous analyses were made:

- An ITT sensitivity analysis was added for 5-year all-cause mortality (Section 9.9.5).
- The cumulative use intervals were further divided to ≤12 months, >12 to 24 months, and >24 months.
- Table added to display the covariate balance between roflumilast exposed and unexposed in standardised mean differences. Only matched patients were included. Covariate balances were reported -1, 1, 2, 3 and 4 years after the CED.
- Additional analysis was added to further balance the adjusted Cox regression model (Section 9.9.5).
- An analysis was added to describe hospitalisation before recent use exposure (Section 9.9.5).
- References to minimally adjusted HR model removed from the table templates and text.
- Additional sensitivity analysis for new diagnosis of malignant neoplasms was conducted where only the first year of the follow-up period was taken into account.
- An analysis was added for extended cumulative exposure for 5-year all-cause mortality, for 5-year follow-up, and early discontinuation design (Section 9.9.5).
- An analysis was added for ever-versus-never use of roflumilast according to the yearly follow-up time period within a single model (Section 9.9.5)
- For malignant neoplasm outcomes only ever use and cumulative exposure durations were retained. Time since discontinuation analyses were removed from the table templates.

The study was conducted as specified in the study protocol and in the SAP. The study protocol was written by following the ENCePP Code of Conduct (ENCePP 2015). The study protocol also followed the key elements of the Guideline for Good Pharmacoepidemiology Practices by the International Society for Pharmacoepidemiology (ISPE 2008). The study was registered on the ENCePP's E-register.

Several measures were employed to ensure the acceptable quality of the data extracts and analyses:

- All data extracts and analyses were fully documented and logged (reproducible).
- The output was produced by programs without further manipulation (manual handling) of data, as fully edited tables, generated by the program, for reproducibility and to avoid transcription errors.
- Data analyses were repeated by a second qualified researcher with requirement of results match, or an independent, qualified researcher reviewed all programs used for data analysis.
- All programs were documented with version control and made available for audits and inspections.

9.9.7.4 Amendment 2 of the Core Statistical Analysis Plan

Date: 15 March 2018

The following changes to the previous analyses were made:

- Subgroup analyses among patients with TIS of 4 who had at least one moderate or severe COPD exacerbation in the year before cohort entry, and the group of patients not fulfilling this definition, were not to be conducted.
- Despite PS matching, potentially higher COPD severity in the roflumilast-exposed patients compared to unexposed patients can cause residual confounding by COPD severity. The following adjustments to existing analyses and additional sensitivity analyses were made to address residual confounding by COPD severity:
  - In the analysis of primary outcome, the adjusted Cox model regression analyses were to be adjusted for markers of COPD severity and healthcare utilisations and general health (Core SAP Section 9.4.1.2.1)
  - In the analysis of secondary and exploratory outcomes, the Cox model regression analyses were to be adjusted for outcome-specific predefined adjusting variables (Core SAP Section 9.4)
  - Selection bias may occur if patients who receive roflumilast within 6 months after launch are significantly different from those who initiate the product after 6 months of launch (early adopter bias). A sensitivity analysis on patients who did not initiate roflumilast treatment within 6 months after launch was added (Core SAP Section 9.4.2.7).
  - The MR is highly dependent on age. In this sensitivity analysis patients with age over 80 at CED were to be excluded (Core SAP Section 9.4.2.8).
- In the 1st interim report, 40 to 50% of roflumilast-exposed patients were observed to have only 1-3 dispensations, with many discontinuing use after the 1st dispensation. The following adjustments to existing analyses and additional sensitivity analyses were done to address the effect of early discontinuation (Core SAP Section 9.4.2.6):

- Sensitivity analysis for the primary outcome and never – ever roflumilast exposure in which patients were required to have at least 2 dispensations within 6 months (180 days) from CED in order to be included as ever exposed in the analyses. CED will be moved 180 days forward and matched strata without at least one exposed and one unexposed was to be removed.
- Sensitivity analyses for the primary outcome with never – ever and cumulative duration exposure definitions were conducted censoring exposed patients at their first roflumilast discontinuation. Discontinuation of roflumilast in this analysis was defined as the time point at which the roflumilast "time since discontinuation" exposure definition first reached status "1-89" and all follow-up time from that time point onwards was removed from the analysis. The primary roflumilast exposure definition, which employed the 50% gap extension was used to define the discontinuation. To maintain balance across cohorts, due to potentially informative censoring, unexposed matches were censored at the time when their exposed match discontinued roflumilast use.
- Reasons for having only 1 roflumilast prescription/dispensation was to be explored using descriptive statistics. Specifically, patients with only one prescription/dispensation were described at the date when their roflumilast exposure ended, or at their last date of follow-up, whichever came first. Among these patients, the number and proportion of the following were reported: i) those alive and not currently in a hospital, ii) those alive and currently in a hospital iii) those who were dead. In addition, among patients with only 1 roflumilast dispensation, the proportion of patients having any of the secondary outcomes prior to roflumilast exposure discontinuation (ie, during current use of the 1st and only prescription) was reported, separately for each secondary outcome.

- As part of investigations related to Cox proportional hazards assumption check, the following analyses were to be performed if deemed necessary. If not conducted, sufficient data on Cox proportional hazard assumptions test results, together with justification why these analyse were not relevant, should be provided (SAP Section 9.4.2.9).
  - Analyses using data from the 1st year of follow-up only. This analysis was used to produce risk estimates for the time immediately after roflumilast initiation. All patients were censored at the time when they reached 1 year of follow-up time. Never-ever and current-recent-past roflumilast exposure definitions were used in these analyses.
  - Analyses using data from the 2nd year of follow-up only. Time scale in these analyses were time since start of 2nd year of follow-up. All matched strata without at least one exposed and one unexposed at the start of 2nd year of follow-up were removed from these analyses. All patients were censored at the time when they reached 2 years of follow-up time. Never-ever and current-recent-past roflumilast exposure definitions were used in these analyses. This analysis was used to investigate if 1st and 2nd year exposure effects might be different, using data from all yearly cohorts.
  - Analyses using data after the 2nd year or follow-up. This analysis was used to produce risk estimates for the later follow-up years (3rd, 4th and 5th) for which data were not available from all yearly cohort until the final report. Time scale in these analyses was time since start of 3rd year of follow-up. All matched strata without at least one

exposed and one unexposed at the start of 3rd follow-up year were removed from these analyses. All patients were censored at the time when they reached 5 years of follow-up time. Never-ever and current-recent-past roflumilast exposure definitions were used in these analyses.

- Analyses in which roflumilast exposure effects for never-ever and current-recent-past could have varied based on accumulated cumulative exposure duration. For the never-ever and current-recent-past exposures, one effect was allowed until 12 months of cumulative exposure duration was reached, and another after 12 months of cumulative exposure duration had been reached. In these analyses, the never-ever and current-recent-past exposure categories were redefined (re-parametrized) based on the cumulative exposure duration variable. The resulting exposure categories were as follows:
  - Never – ever analysis
    - Ever, under 12 months of cumulative duration
    - Ever, over 12 months of cumulative duration
  - Current-recent-past analysis:
    - Current, under 12 months of cumulative duration
    - Recent, under 12 months of cumulative duration
    - Past, under 12 months of cumulative duration
    - Current, over 12 months of cumulative duration
    - Recent, over 12 months of cumulative duration
    - Past, over 12 months of cumulative duration
- The Kaplan-Meier estimator was also plotted for exposed patients who discontinued roflumilast prior to and after reaching 12 months of cumulative exposure duration. The time scale in these analyses was time since exposed patient's first discontinuation. For the unexposed patients, the corresponding follow-up start point was derived from the matched exposed patient's time of first discontinuation, and only those unexposed who had matched exposed with discontinuation were used. Strata without at least one exposed and unexposed at the time of exposed patient's discontinuation were excluded. Both the exposed and unexposed matched patients were censored if exposed re-started roflumilast. This analysis explored mortality among patients who discontinued roflumilast after a short usage period versus long usage period.

- The effect of asthma was investigated in subgroup analyses among patients with and without asthma. After creating each of these two subgroups based on the asthma status, matched strata without at least one exposed and unexposed were removed. Patients background statistics and balance analysis was performed prior to making outcome analyses (MRs, rate ratios, crude and adjusted HRs and Kaplan-Meier plots). The rationale for these analyses was that patients with both asthma and COPD diagnoses were included in the study but the classification between asthma and COPD by physicians is difficult. In addition, roflumilast is unique therapy specifically for COPD, and hence asthma as a potential effect modifier may have played an important role in the findings of the 1st interim report.

- In Section 7.2, roflumilast exposure variable "time since discontinuation" was changed so that current users are a separate category from those having discontinuation within 1 to 89 days.
- In Section 9.4.2.6, the effect of the number of roflumilast dispensations was addressed in an analysis employing an alternative cumulative dose analysis. In particular, roflumilast exposure was based on the number of dispensations: "0" for never exposed and "1" from the time of first roflumilast dispensing onwards until the second dispensing, "2" from the time of the second dispensing until third dispensing and so forth. This time-dependent exposure variable was categorized prior to analyses as follows: "0," "1," "2-3," "4-9" and ">9." In addition to these formal analyses, the total number of DDDs dispensed per patient was summarized among patients with 1, 2-3, 4-9, and 10 or more roflumilast dispensations over the whole follow-up, i.e., the total count of DDDs per patient at the end of follow-up was presented, stratified by number of dispensations.

In addition, text clarifications were made to avoid ambiguity leading potentially to different methods across the 3 study countries.

9.9.7.5 Amendment 1 of the Core Statistical Analysis Plan

Date: 06 May 2017

The following changes to the previous analyses were made:

- TIS values were amended not to combine TIS values 3 and 4 into one category
- Clarification regarding future safety signal evaluations was made to indicate that such evaluations will be conducted in all interim analyses
- Analyses performed for potential identified safety signals related to 5-year all-cause mortality were amended to include stratified analyses of 5-year all-cause MRs and 5-year all-cause MRR with 95% CI. Briefly, these stratified analyses were to consider the subpopulation of patients deemed most relevant for roflumilast use (TIS equal to 4 with exacerbations in the 12 months before CED, eg, patients with the most severe COPD) and those not fulfilling this definition (TIS under 4 or no exacerbations in the 12 months before CED, eg, patients with less severe COPD). Further safety signal evaluation was to be conducted for the relevant subpopulation. These changes were also applied to secondary endpoints, however IRs and IRR with 95% CI were calculated for current use of roflumilast for all secondary endpoints excluding those related to malignant neoplasms, wherever use of roflumilast was considered the relevant use category. In cases where a safety signal for a primary or secondary outcome was present in the relevant subpopulation of patients, crude and adjusted HR were calculated by Cox regression analysis. Since for the subpopulations balance by PS matching could no longer be assumed (in contrast to the full cohort), balance analysis was conducted for important parameters of COPD severity or for risk factors of the respective secondary endpoint using standardized differences and adjustment by deciles of the PS was additionally performed in the Cox regression analysis.

10. RESULTS

The results presented here are for GER, SWE, and the US. At the time of the final study report, results from NOR were unavailable. Outputs from NOR will be provided as soon as they become available.

10.1 Participants

The total number of PS-matched patients per year and per country are shown in Table 11.

In GER for 2011 to 2013, 9325 roflumilast-exposed patients and 2184053 unexposed patients met the inclusion criteria. After matching, the study population of the 3 annual cohorts included 50567 patients, with 8783 roflumilast-exposed patients matched with 41784 matched unexposed patients. Over half of the patients were identified in the 2011 cohort (28916 patients), which also included some patients who started roflumilast in August to December 2010 and matched unexposed during the same period. Note that in Table 11, the number of matched patients is higher than reported in Table 16 and Section 10.4.1 and Section 10.5.1, as some patients had to be excluded post-hoc due to an update of the database.

In SWE for 2011 to 2013, 3249 patients ever exposed to roflumilast and 478047 unexposed patients met the inclusion criteria. After matching, the study population of the 3 annual cohorts included 19025 patients, with 3234 roflumilast-exposed patients matched with 15776 unexposed patients. Most patients were identified in 2011 and 2012, with the lowest number of patients identified in 2013.

In the US for 2011 to 2013, 9598 patients ever exposed to roflumilast and 1669950 unexposed patients met the inclusion criteria. After matching, the study population of the 3 annual cohorts included 56792 patients, with 9598 roflumilast-exposed patients matched with 47151 unexposed patients. Nearly half of the study population was in the 2012 cohort (26299 patients total; with 4451 roflumilast exposed and 21829 unexposed patients).

Table 11 Patient Accrual Per Country and Study Year

	GER				SWE				US			
Year	**2011**	**2012**	**2013**	**All**	**2011**	**2012**	**2013**	**All**	**2011**	**2012**	**2013**	**All**
No of patients in study population (PS matched cohort)	28916	11697	9954	50567	7581	7124	4320	19025	13160	26299	17333	56792
No of roflumilast-exposed patients with matches	4959	2061	1763	8783	1293	1210	731	3234	2220	4451	2927	9598
No of unexposed patients	23957	9636	8191	41784	6281	5909	3586	15776	10924	21829	14398	47151
No of roflumilast-exposed patients without matches	166	215	161	542	7	5	3	15	16	19	8	43
No of patients counted twice[a]	0	707	695	1402	0	348	260	608	0	750	887	1637

[a] The number of patients counted twice is the number of controls who became exposed during 2012 or 2013 and were included as exposed in that year, after having already been included as unexposed in a previous annual cohort (2011 or 2012). Their follow-up as unexposed in the earlier cohort was terminated when they switched to roflumilast, as dictated by the protocol

GER = Germany; PS = propensity score; SWE = Sweden; US = United States

Sources: Appendix 1 Table 1; Appendix 2.1 Table 1; Appendix 3.1 Table 1

In the full study cohort including all CE years, 86.27%, 93.75%, and 95.49% of exposed patients were matched with 5 unexposed controls in GER, SWE, and the US, respectively (Table 12).

Table 12 Distribution of the Number of Matches

	0		1		2		3		4		5		
All years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**Total**
GER	542	5.81	296	3.17	174	1.87	157	1.68	111	1.19	8045	86.27	9325
SWE	15	0.46	24	0.74	43	1.32	48	1.48	73	2.25	3046	93.75	3249
US	43	0.45	61	0.63	82	0.85	100	1.04	149	1.55	9206	95.49	9641

GER = Germany, N = number of patients; SWE = Sweden, US = United States
Sources: Appendix 1 Table 12; Appendix 2.1 Table 2; Appendix 3.1 Table 2

In GER, SWE, and the US, 1402, 608, and 1637 patients, respectively, were controls in a prior annual cohort and became matched exposed patients in a later annual cohort upon exposure to roflumilast. Their follow-up as unexposed in the prior annual cohort was terminated at that point.

The age and sex distribution per country before and after matching are shown in Table 13. After PS matching, age and sex were balanced with only negligible differences between the roflumilast-exposed and unexposed cohorts per country. In comparison between countries, patients were of younger age in GER than in SWE and the US. Particularly in the oldest age group aged 80+, percentages were lower in GER than in SWE or the US. A higher percentage of patients were male in GER than in SWE or the US.

Table 13 Age and Sex Distribution at Cohort Entry in The Ever and Never Exposure Cohorts Before and After PS Matching

	Before matching						After matching					
	GER		SWE		US		GER		SWE		US	
	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never
	N (%) n=9325	N (%) n=2184053	N (%) n=3249	N (%) n=478047	N (%) n=9641	N (%) n=1669950	N (%) n=8783	N (%) n=41784	N (%) n=3234	N (%) n=15776	N (%) n=9598	N (%) n=47151
Age at CED												
40-44	80 (0.86)	121937 (5.68)	10 (0.31)	4408 (0.92)	19 (0.20)	19466 (1.17)	75 (0.85)	344 (0.82)	10 (0.31)	43 (0.27)	19 (0.20)	99 (0.21)
45-49	262 (2.81)	197740 (9.05)	26 (0.80)	12273 (2.57)	85 (0.88)	41976 (2.51)	250 (2.85)	1193 (2.86)	26 (0.80)	129 (0.82)	80 (0.83)	475 (1.01)
50-54	566 (6.07)	229501 (10.51)	85 (2.62)	21355 (4.47)	226 (2.34)	74182 (4.44)	530 (6.03)	2422 (5.80)	84 (2.60)	373 (2.36)	221 (2.30)	1147 (2.43)
55-59	1039 (11.14)	249007 (11.40)	184 (5.66)	35786 (7.49)	561 (5.82)	111131 (6.65)	972 (11.07)	4584 (10.97)	183 (5.66)	899 (5.70)	552 (5.75)	2818 (5.98)
60-64	1462 (15.68)	258368 (11.83)	439 (13.51)	59904 (12.53)	1110 (11.51)	185882 (11.13)	1347 (15.34)	6481 (15.51)	436 (13.48)	2082 (13.20)	1102 (11.48)	5784 (12.27)
65-69	1800 (19.30)	253571 (11.61)	768 (23.64)	84828 (17.74)	1789 (18.56)	249856 (14.96)	1672 (19.04)	7692 (18.41)	766 (23.69)	3654 (23.16)	1784 (18.59)	8938 (18.96)
70-74	1953 (20.94)	325875 (14.92)	714 (21.98)	77764 (16.27)	2,222 (23.05)	291232 (17.44)	1846 (21.02)	8954 (21.43)	712 (22.02)	3541 (22.45)	2219 (23.12)	10999 (23.33)
75-79	1216 (13.04)	247181 (11.32)	552 (16.99)	70506 (14.75)	1985 (20.59)	293340 (17.57)	1168 (13.30)	5635 (13.49)	549 (16.98)	2750 (17.43)	1979 (20.62)	9534 (20.22)
80+	947 (10.16)	300873 (13.78)	471 (14.50)	111223 (23.27)	1644 (17.05)	402885 (24.13)	923 (10.51)	4479 (10.72)	468 (14.47)	2305 (14.61)	1642 (17.11)	7357 (15.60)
Range (min, max)	(41, 98)	(41, 107)	(40, 95)	(40, 107)	(40, 85)	(40, 85)	(41, 98)	(41, 98)	(40, 95)	(40, 96)	(40, 85)	(40, 85)

Table 13 Age and Sex Distribution at Cohort Entry in The Ever and Never Exposure Cohorts Before and After PS Matching

	Before matching						After matching					
	GER		SWE		US		GER		SWE		US	
	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never
	N (%) n=9325	N (%) n=2184053	N (%) n=3249	N (%) n=478047	N (%) n=9641	N (%) n=1669950	N (%) n=8783	N (%) n=41784	N (%) n=3234	N (%) n=15776	N (%) n=9598	N (%) n=47151
Mean (±SD)	67.49 (9.57)	64.87 (12.86)	70.91 (8.43)	71.25 (10.96)	71.23 (8.37)	70.93 (10.38)	67.61 (9.60)	67.72 (9.60)	70.90 (8.41)	71.04 (8.39)	71.27 (8.34)	70.88 (8.33)
Median	68.00	65.00	71.00	71.00	72.00	72.00	68.00	68.00	71.00	71.00	72.00	72.00
Q1	61.00	54.00	66.00	64.00	66.00	64.00	61.00	61.00	66.00	66.00	66.00	65.00
Q3	74.00	75.00	77.00	79.00	77.00	79.00	74.00	74.00	77.00	77.00	77.00	77.00
Sex												
Male	5218 (55.96)	970766 (44.45)	1400 (43.09)	210563 (44.05)	4994 (51.80)	788671 (47.23)	4891 (55.69)	23178 (55.47)	1393 (43.07)	6761 (42.86)	4983 (51.92)	24504 (51.97)
Female	4107 (44.04)	1213287 (55.55)	1849 (56.91)	267484 (55.95)	4647 (48.20)	881244 (52.77)	3892 (44.31)	18606 (44.53)	1841 (56.93)	9015 (57.14)	4615 (48.08)	22647 (48.03)

CED = cohort entry date; GER = Germany; Min = minimum; Max = maximum; N = number of patients per parameter; n = number of patients in overall population; PS = propensity score; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SWE = Sweden; US = United States.

Sources: Appendix Table 3d, Table 6; Appendix 2.1 Table 3; Appendix 3.1 Table 3

The outcome of matching based on the PS variables listed in Table 7 is graphically presented in Figure 2 for each country. Before matching, the logits of the PS values for the roflumilast-exposed and unexposed cohorts show that the likelihood of patients in the 2 cohorts to start roflumilast was very different. After matching, the probability distribution to start roflumilast became similar in matched exposed and unexposed patients. However, for higher logit values (higher likelihood of being treated for COPD), differences between exposed and unexposed patients remained, with more patients with a higher disease severity being included in the exposed cohort in all 3 countries.

Figure 2 PS Distribution of Roflumilast Exposed and Unexposed Patients Before and After Matching Including All Study Years

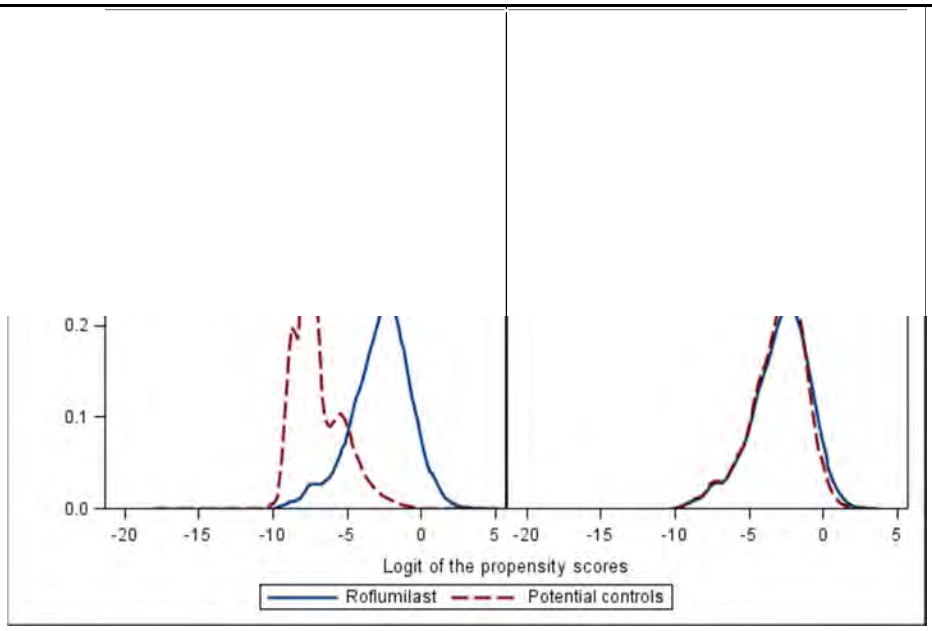
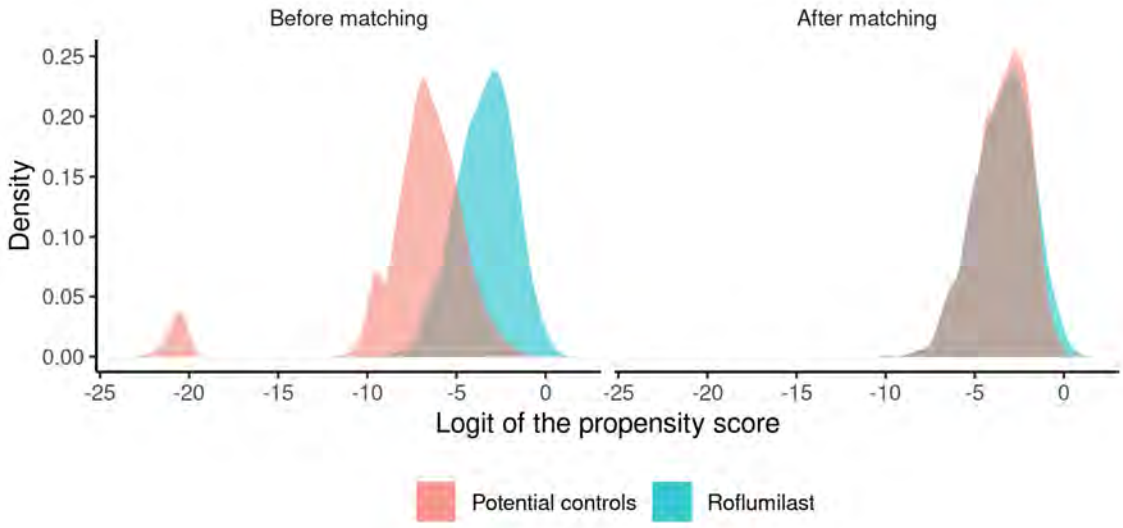
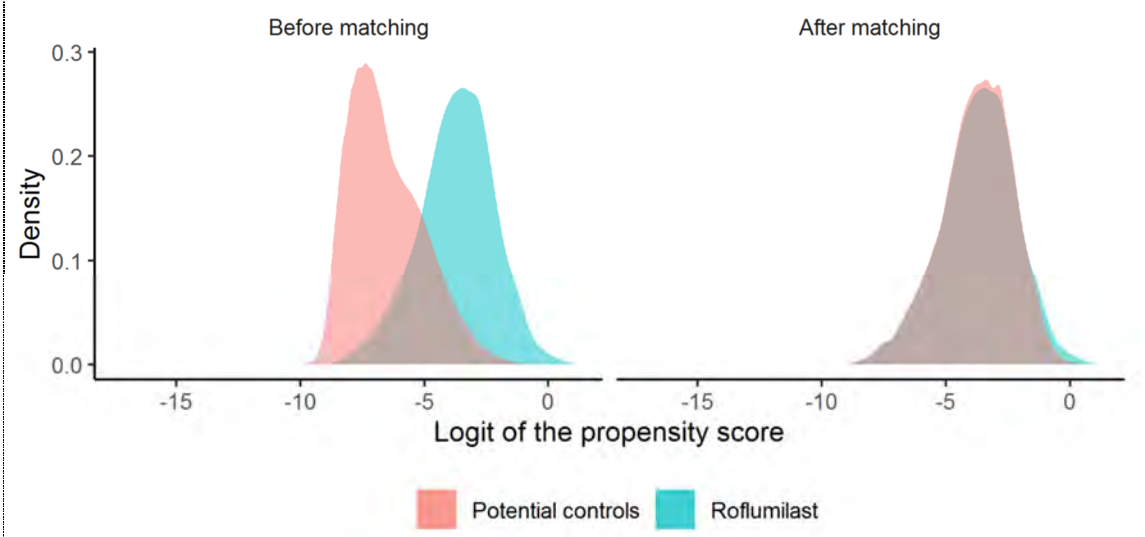
	Before Matching	After Matching
GER		
SWE		

Figure 2 PS Distribution of Roflumilast Exposed and Unexposed Patients Before and After Matching Including All Study Years

	Before Matching	After Matching
US		

GER = Germany; PS = propensity score; SWE = Sweden; US = United States.
Source: Appendix 1 Figure 1d; Appendix 2.3 Figure 3

The residual imbalance in COPD severity is further reflected in the standardised differences for the PS variables before and after matching, summarised in Table 14 listing variables imbalanced above the predefined threshold of 0.1 standardised difference.

In GER, one variable (TIS = 1) remained imbalanced in the 2013 entry cohort and 2 variables, number of hospitalisations due to COPD exacerbation in the 12 months before CED and number of moderate COPD exacerbations in the 12 months before CED, remained imbalanced after matching across all years. While 28% of the matched exposed patients were hospitalised at least once for COPD in the 12 months prior to CED and 4% were hospitalised 3 or more times, fewer patients were hospitalised in the unexposed cohort (24% at least once and 2% three or more times in the year prior to CED). Also, the number of patients with 3 or more exacerbations within 12 months prior to CED was substantially higher in matched exposed patients (51%) compared to the matched unexposed controls (45%) (see Appendix 1, GER Table 3a). A number of COPD-related variables remained imbalanced below the 0.1 threshold (discussed further below).

In SWE, 31 out of 79 variables were imbalanced before matching, but only 3 variables (number of hospitalisations due to COPD exacerbation in the 30 days before CED, number of hospitalisations due to COPD in the 12 months before CED, SABA/SAMA use in the last 4 months before CED) remained imbalanced in the all-years cohort after matching. Consequently, more roflumilast-exposed unmatched patients (86.7%) had hospitalisations due to COPD exacerbation in the 30 days before CED than roflumilast-exposed matched patients (11.9%) (see Appendix 2.1, SWE Table 5). In addition, minor imbalances not reaching the

predefined threshold of 0.1 remained in some markers of COPD disease severity (discussed further below), indicating that the exposed cohort still had a slightly higher COPD severity.

In the US, after matching, several PS variables exceeded the standardised difference threshold of 0.1 between roflumilast-treated and untreated patients in each annual cohort or in the cohort including all years; however, a number of variables related to COPD severity were still imbalanced just below the threshold of 0.1 (discussed further below), generally indicating higher disease severity in the exposed cohort. In addition, important non-PS variables in a particular country (eg, SABA/SAMA use 4 months before CED in SWE and the US) were imbalanced above the threshold of 0.1, as detailed in Figure 3 and Figure 4.

Table 14 Imbalanced Variables (Standardised Difference >0.1) at CED

	2011 cohort			2012 cohort			2013 cohort			All years cohort		
	GER	SWE	US	GER	SWE	US	GER	SWE	US	GER	SWE	US
Number of hospitalisations due to COPD in the 12 months before CED	-	-	-	-	X	-	-	X	X	X	X	-
Number of emergency room visits due to COPD in the 12 months before CED (US only)	-	-	-	-	-	-	-	-	X	-	-	X
Number of hospitalisations due to COPD in the 30 days before CED	-	X	X	-	X	X	-	X	X	-	X	X
Number of emergency room visits due to COPD in the 30 days before CED (US only)	-	-	-	-	-	-	-	-	X	-	-	X
Number of moderate COPD exacerbations in the 12 months before CED	-	-	-	-	-	-	-	-	-	X	-	-
Treatment intensity score of 1	-	-	-	-	-	-	X	-	-	-	-	-
SABA/SAMA use in the last 4 months before CED	-	X	X	-	X	X	-	X	X	-	X	X

Note: Imbalance defined by a cut-off value of >0.1 in the standardised difference between exposure groups

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; NA = not applicable in this country; SABA = short-acting β_2 agonists; SWE = Sweden; US = United States

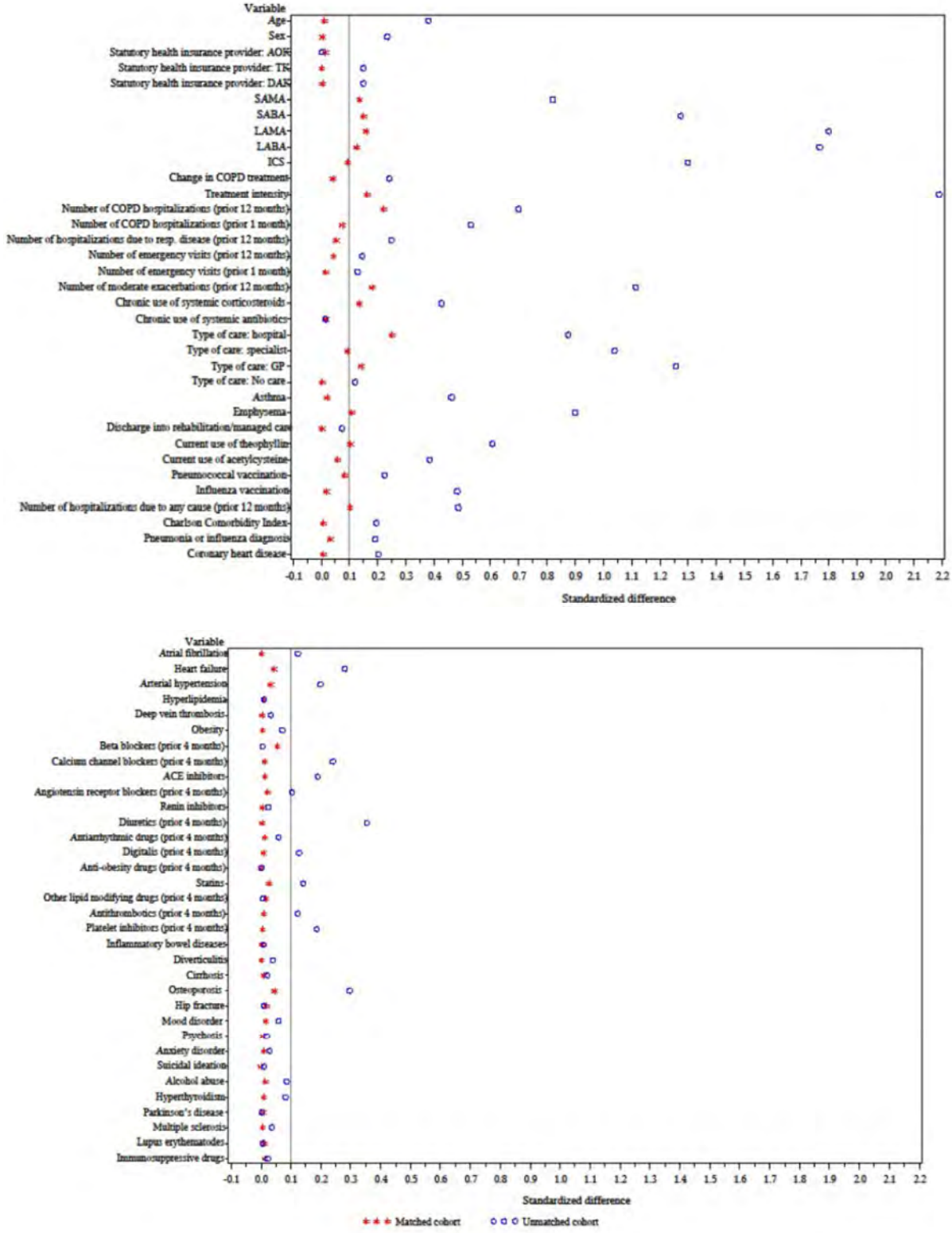
The balance for all PS variables used in any country was further examined. Standardised differences observed at CED-1 and at CED are displayed for GER in Figure 3. Findings for the standardised differences observed at CED and at different years of follow-up are illustrated in Figure 4 and Table 5 for GER, Figure 6 for SWE, and Figure 7 for the US; note that the scales for SWE and US differ compared to GER. Assessment at CED-2 could not be performed in GER and the US because patients were only required to have 1 year of database history prior to CED such that many patients had insufficient data with which to define baseline variables.

When the balance of PS variables was examined over follow-up time for the patients remaining in the exposed and unexposed cohorts, the standardised differences increased substantially in all study countries. Consistently across countries, this divergence between exposed and unexposed cohorts was related to markers of COPD severity such as use of COPD medications other than roflumilast, hospitalisations for COPD exacerbations, etc. In contrast, almost none of the PS variables not directly related to COPD showed differences in the standardised difference above the predefined threshold of 0.1 between the exposed and unexposed cohorts, with the exception of osteoporosis, for which the standardised difference might be increased over time as a result of larger systemic corticosteroid use in more severe COPD patients.

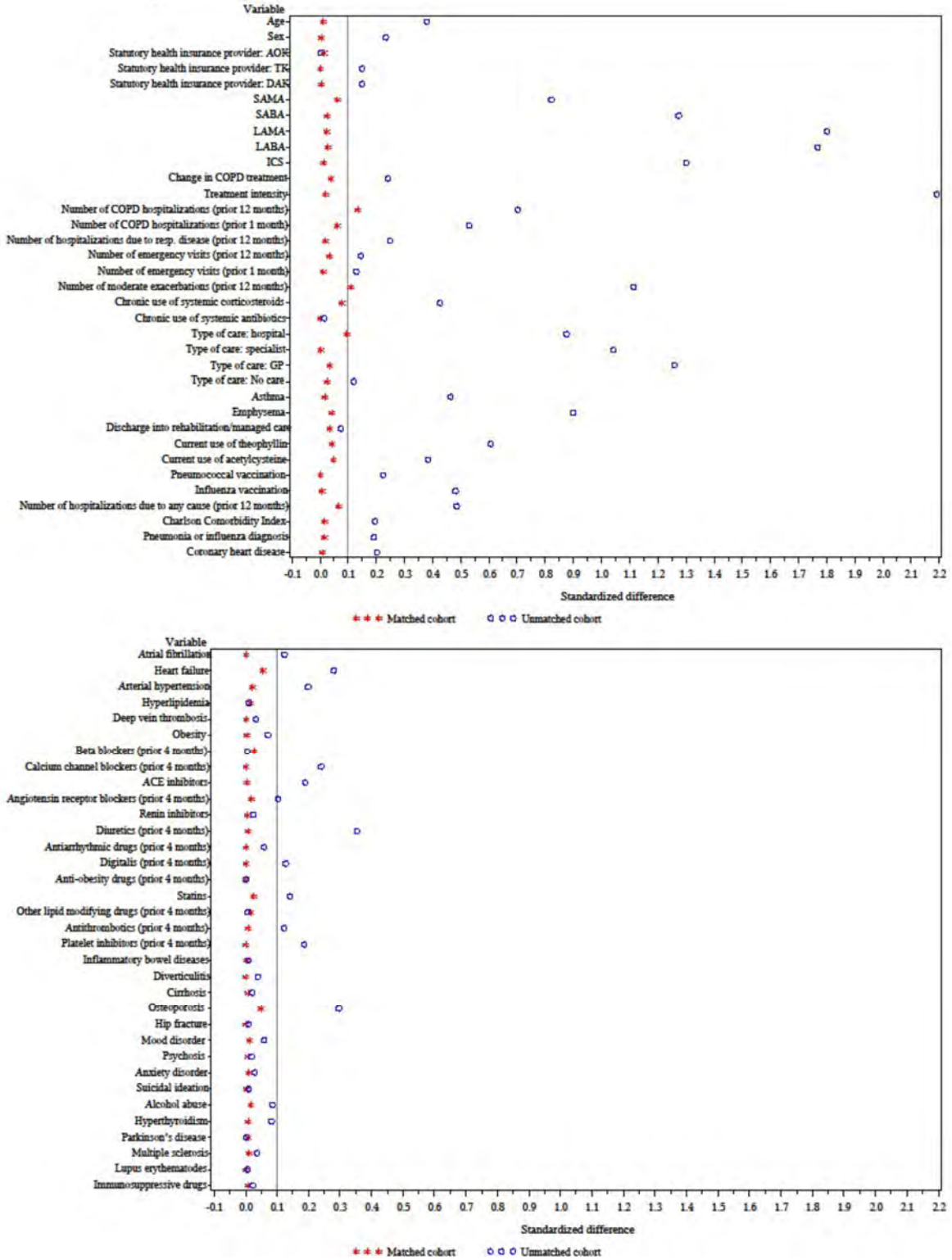
When looking back in time, and evaluating balance for PS variables at CED, at the year prior to baseline (CED-1), and 2 years prior to baseline (CED-2; in SWE only), it was seen that despite matching at baseline and achieving a reasonable balance at baseline, further imbalances in variables related to COPD severity were observed at 1 and 2 years before cohort entry. These findings were consistent across countries, further suggesting that matching at baseline did not balance existing differences in COPD severity between the exposed and unexposed cohort as well as hoped for, despite all efforts.

Figure 3 Standardised Differences for the Propensity Score Variables After Matching at CED-1 and CED for GER

CED-1



At Cohort Entry



ACE = angiotensin-converting enzyme; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist
Source: Appendix 1 Figure 2.a.4 and Figure 2.b

Figure 4 Standardized Differences for the Propensity Score Variables at Different Time-Points for GER

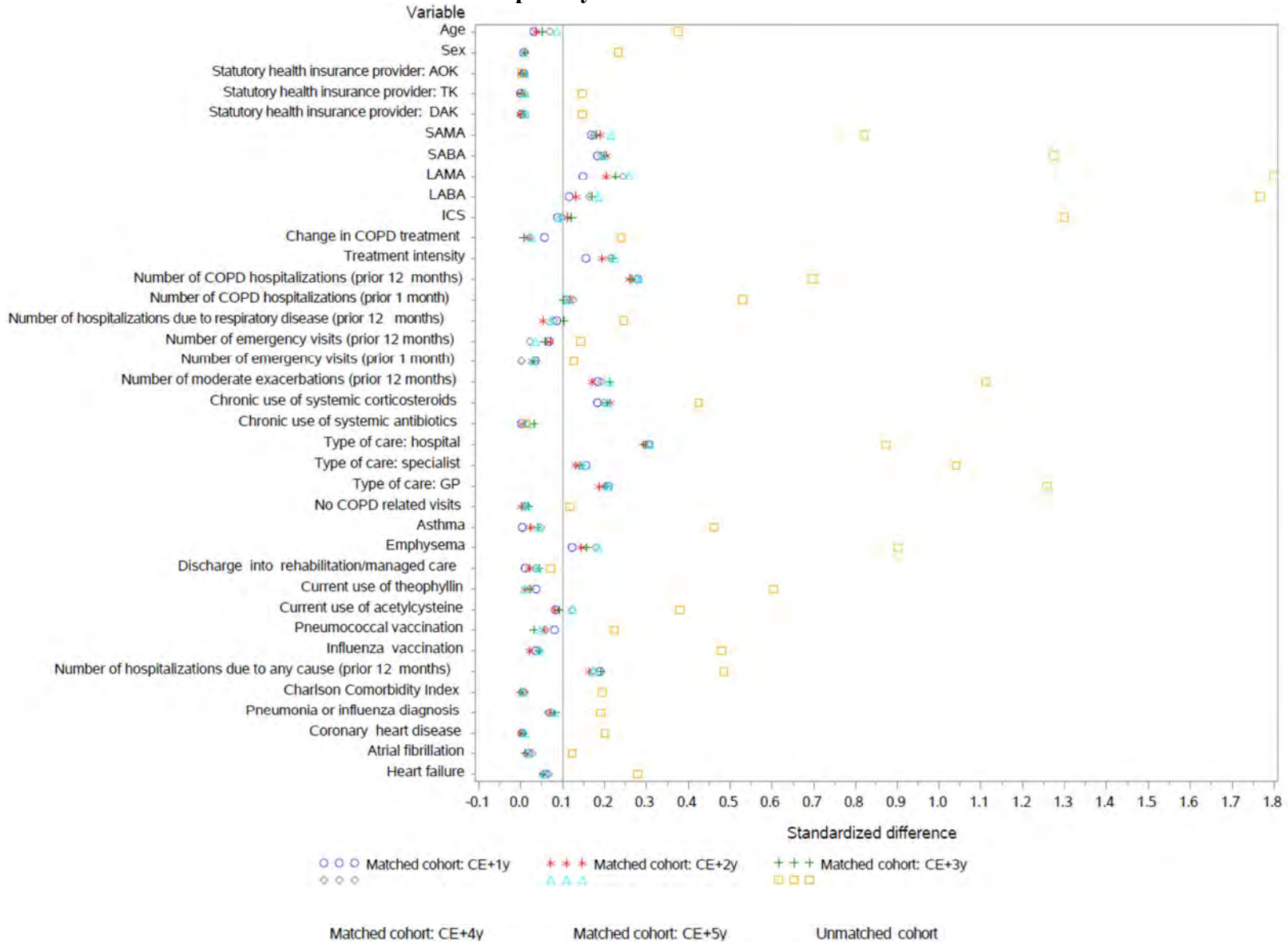
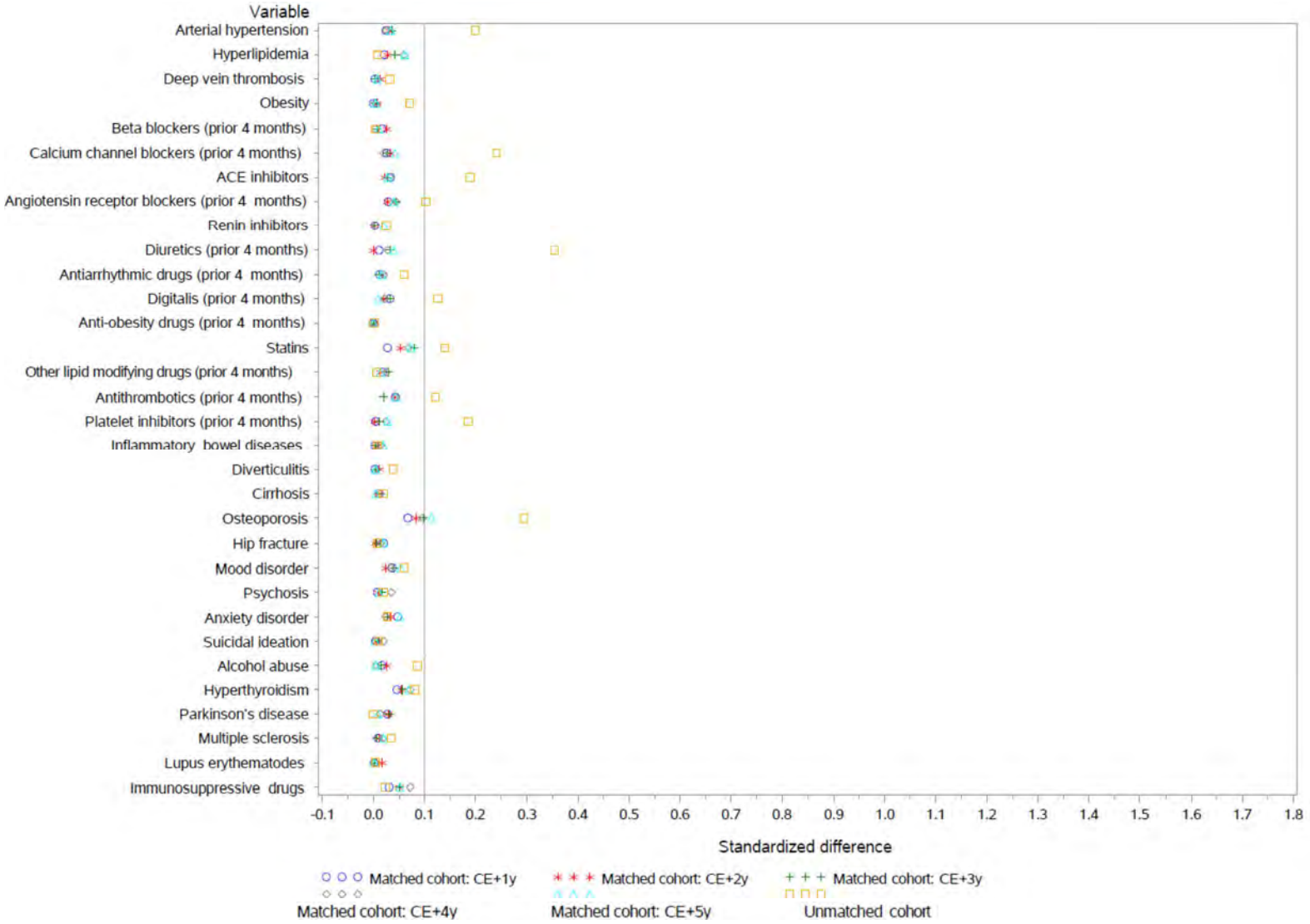
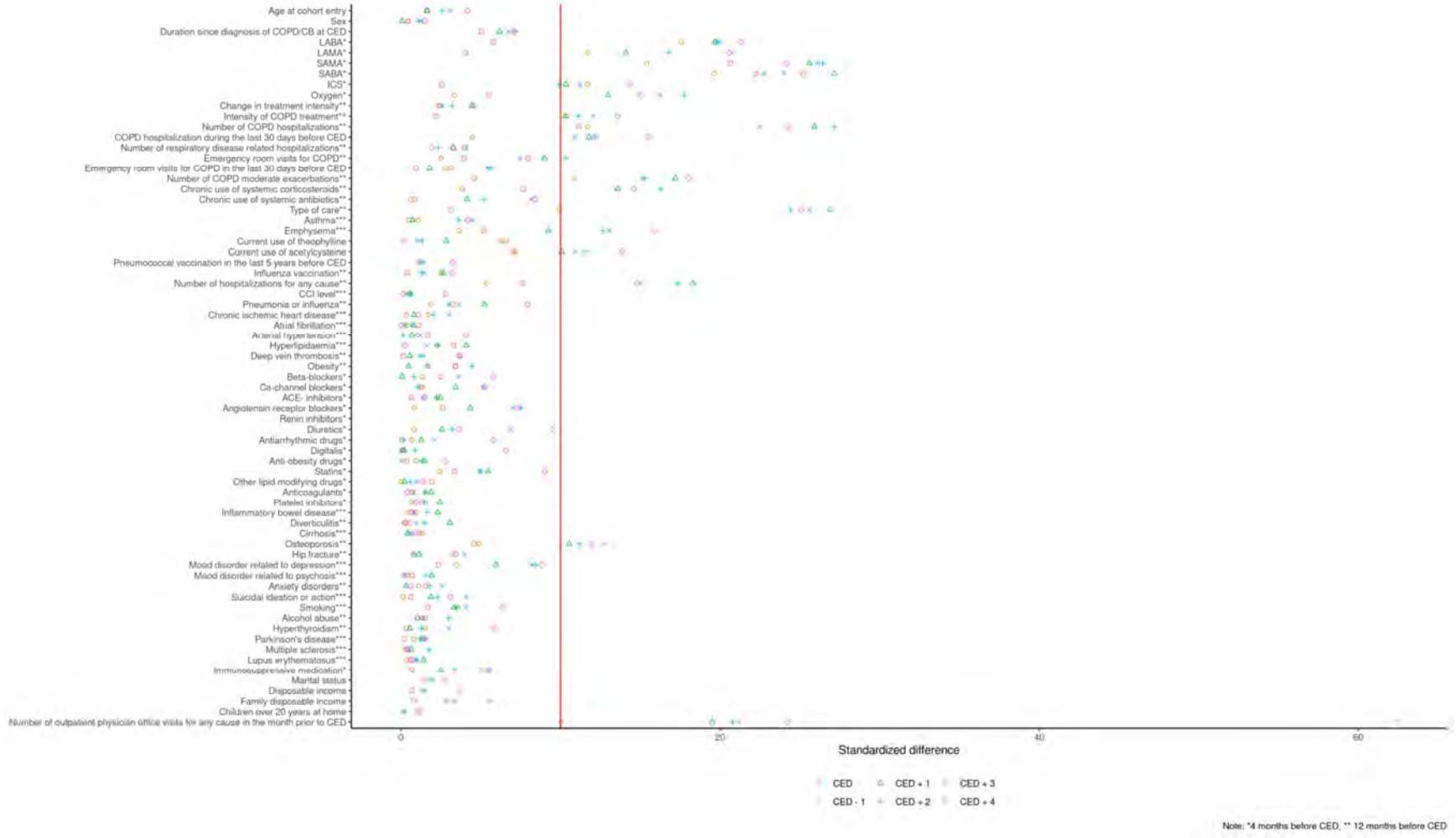


Figure 5 Standardized Differences for the Propensity Score Variables at Different Time-Points for GER (cont'd)



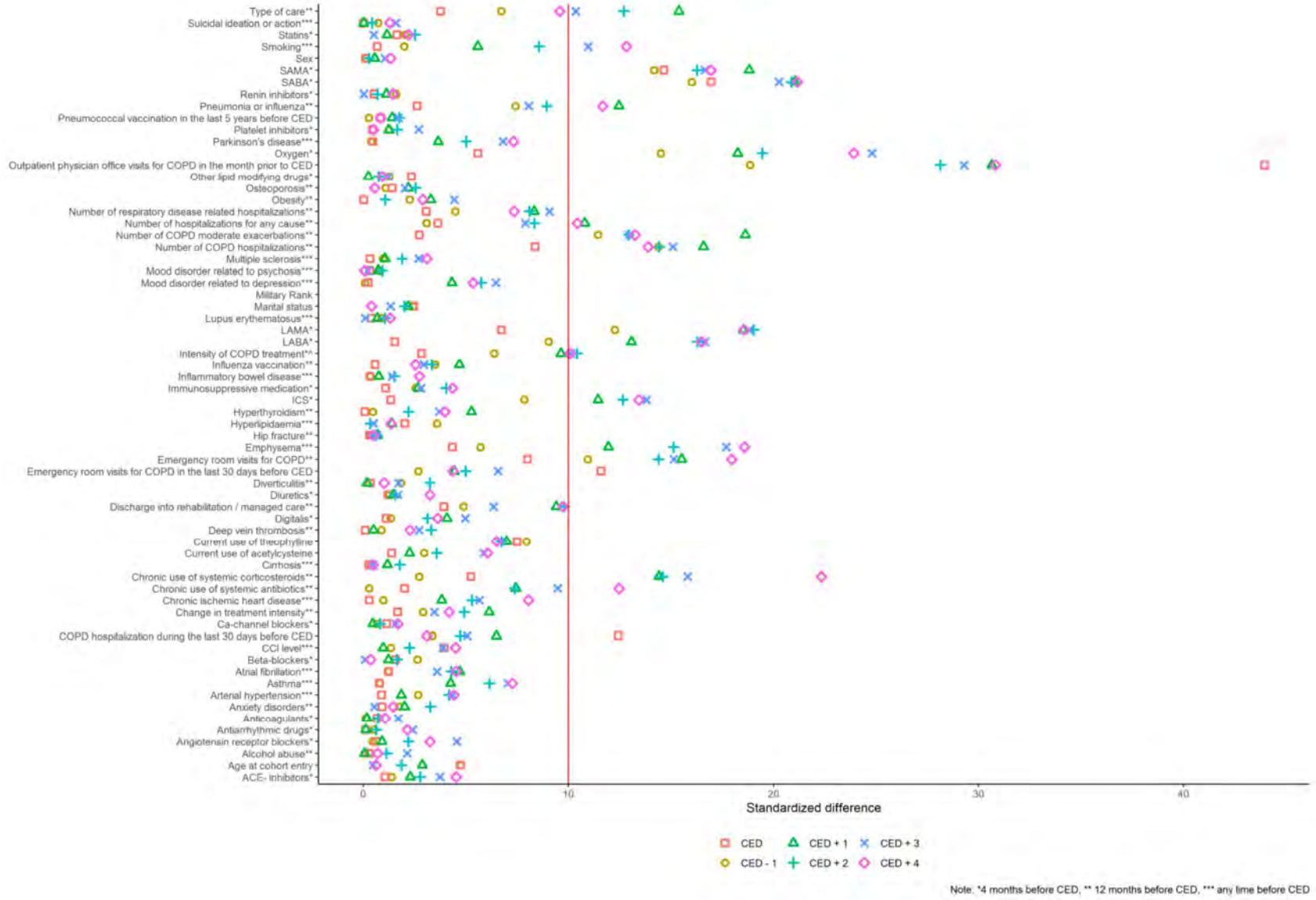
ACE = angiotensin-converting enzyme; CE = cohort entry; COPD = chronic obstructive pulmonary disease; GER = Germany; GP = generic product; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist
Source: Appendix 1 Figure 2H

Figure 6 Standardized Differences for the Propensity Score Variables at Different Time-Points for SWE



ACE = angiotensin-converting enzyme; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GP = general practitioner; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist
Source: Appendix 2.1 Figure 1

Figure 7 Standardized Differences for the Propensity Score Variables Before and After Matching in the US



ACE = angiotensin-converting enzyme; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GP = general practitioner; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist
Source: Appendix 3.1 Figure 1

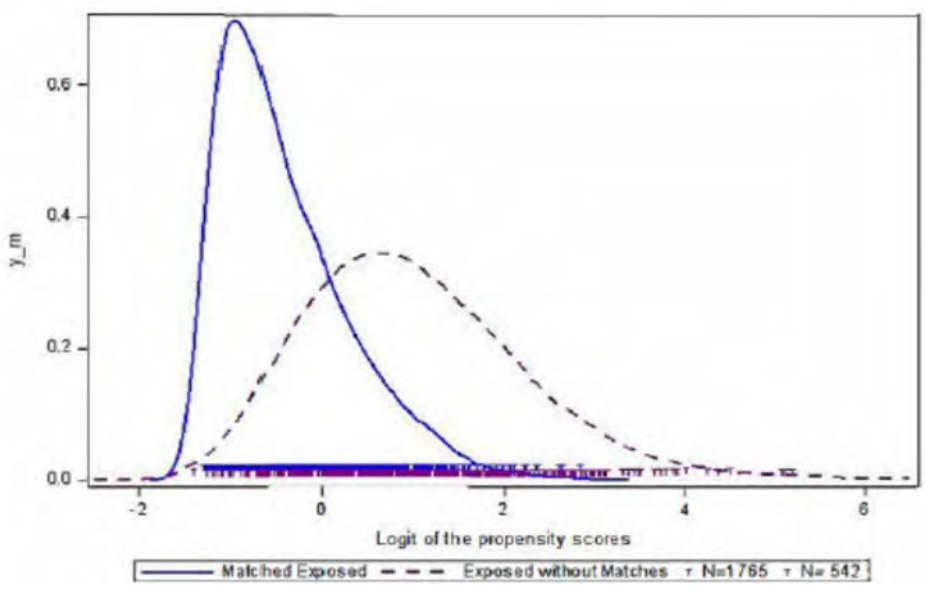
There were 542 roflumilast-exposed patients without matches in GER, 15 in SWE, and 43 in the US who were excluded from the analyses (Table 15). These patients, as expected, were different on average from the roflumilast-exposed matched patients.

To understand how representative the matched exposed patients could be for the unmatched, some analyses were performed to compare these 2 groups. In GER (Figure 8) the distribution of matched and unmatched patients in the fifth PS quintile (the one with highest COPD severity) substantially overlapped, although some higher PS scores (indicating higher COPD severity) were observed in the unmatched exposed. In SWE and the US, the distribution of PS of the matched and unmatched patients showed a higher proportion of unmatched patients than matched patients with higher PS (Figure 9 and Figure 10).

Characteristics of roflumilast-exposed patients with and without matches regarding age, sex and markers of COPD severity are compared in Table 15. Roflumilast-exposed patients without matches were younger and had higher COPD severity than roflumilast-exposed patients with matches. Comorbidity as indicated by the Charlson Comorbidity Index was similar between roflumilast-exposed patients with and without matches in GER. In the US, roflumilast-exposed patients without matches were younger, more commonly female, and subject to more comorbidities than patients with matches. Notably, patients without matches had more severe COPD than those with matches according to several metrics such as emergency room visits in the 30 days or 1 year before CED, hospitalisations for respiratory-related causes, COPD exacerbations, and TIS. A particular high discrepancy was observed for hospitalisations due to COPD exacerbation in the 30 days before CED. In all 3 countries, exposed patients without matches all fell within the highest PS quintile.

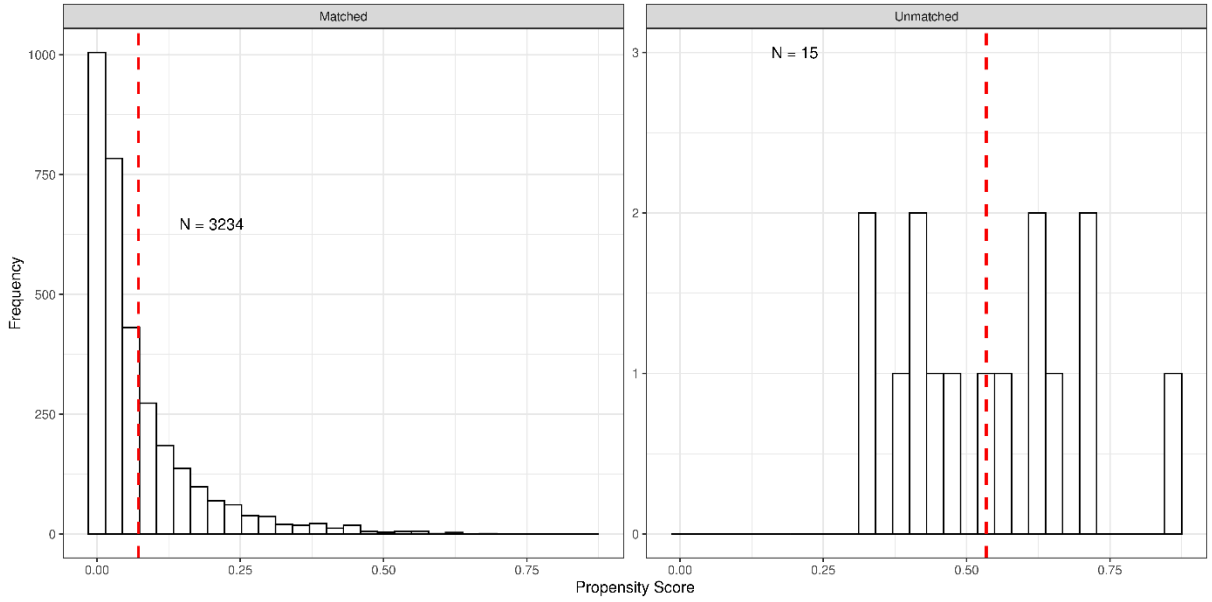
Figure 8 PS Distribution of Roflumilast Exposed Matched and Unmatched Patients in the Fifth PS Quintile Including All Study Years in GER

GER



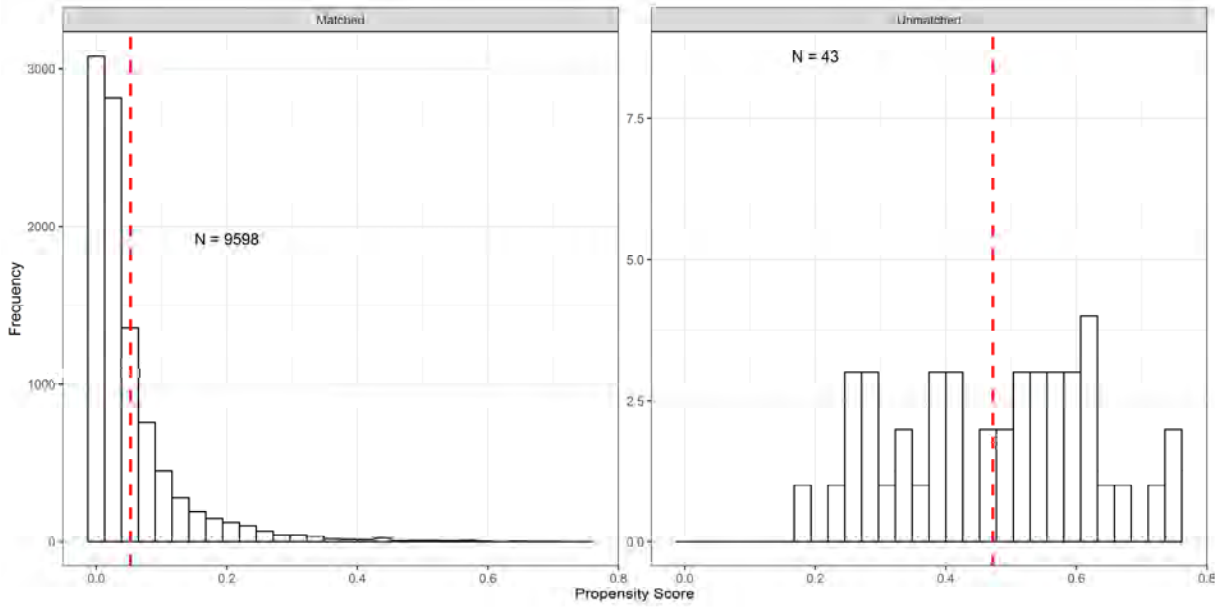
GER = Germany; N = number of patients.
Source: Appendix 1 Figure 1E

Figure 9 PS Distribution of Roflumilast Exposed Matched and Unmatched Patients Including All Study Years in SWE



N = number of patients; SWE = Sweden.

Figure 10 PS Distribution of Roflumilast Exposed Matched and Unmatched Patients Including All Study Years in the US



N = number of patients; US = United States.

Table 15 Age, Sex and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients

	GER		SWE		US	
	Exposed with matches	Exposed without matches	Exposed with matches	Exposed without matches	Exposed with matches	Exposed without matches
	N (%) (n=8783)	N (%) (n=542)	N (%) (n=3234)	N (%) (n=15)	N (%) (n=9598)	N (%) (n=43)
Age						
40-44	75 (0.85)	5 (0.92)	10 (0.31)	NA	19 (0.20)	NA
45-49	250 (2.85)	12 (2.21)	26 (0.80)	NA	80 (0.83)	5 (11.63)
50-54	530 (6.03)	36 (6.64)	84 (2.60)	1 (6.67)	221 (2.30)	5 (11.63)
55-59	972 (11.07)	67 (12.36)	183 (5.66)	1 (6.67)	552 (5.75)	9 (20.93)
60-64	1347 (15.34)	115 (21.22)	436 (13.48)	3 (20.00)	1102 (11.48)	8 (18.60)
65-69	1672 (19.04)	128 (23.62)	766 (23.69)	2 (13.33)	1784 (18.59)	5 (11.63)
70-74	1846 (21.02)	107 (19.74)	712 (22.02)	2 (13.33)	2219 (23.12)	3 (6.98)
75-79	1168 (13.30)	48 (8.86)	549 (16.98)	3 (20.00)	1979 (20.62)	6 (13.95)
80+	923 (10.51)	24 (4.43)	468 (14.47)	3 (20.00)	1642 (17.11)	2 (4.65)
Range (min, max)	(41, 98)	(41, 91)	(40, 95)	(53, 90)	(40, 85)	(45, 83)
Mean (SD)	67.60 (9.63)	65.64 (8.41)	70.90 (8.41)	71.70 (11.04)	71.27 (8.34)	62.33 (10.41)
Median (Q1, Q3)	68 (61, 74)	66 (60, 71)	71 (66, 77)	73 (63, 78)	72 (66, 77)	61 (55, 70)
Sex						
Male	4891 (55.69)	327 (60.33)	1393 (43.07)	7 (46.67)	4,983 (51.92)	11 (25.58)
Female	3892 (44.31)	215 (39.67)	1841 (56.93)	8 (53.33)	4,615 (48.08)	32 (74.42)
Number of hospitalisations due to COPD exacerbations in the 12 months prior to CED						
0 1-2 ≥3	6289 (71.60) 2107 (23.99) 387 (4.41)	57 (10.52) 323 (59.59) 162 (29.89)	2183 (67.50) 691 (21.37) 360 (11.13)	NA NA 15 (100.00)	7725 (80.49) 1765 (18.39) 108 (1.13)	5 (11.63) 25 (58.14) 13 (30.23)
Hospitalisation due to COPD exacerbation in the 30 days before CED	902 (10.27)	357 (65.87)	384 (11.87)	13 (86.67)	456 (4.75)	31 (72.09)

Table 15 Age, Sex and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients

	GER		SWE		US	
	Exposed with matches	**Exposed without matches**	**Exposed with matches**	**Exposed without matches**	**Exposed with matches**	**Exposed without matches**
	N (%) (n=8783)	**N (%) (n=542)**	**N (%) (n=3234)**	**N (%) (n=15)**	**N (%) (n=9598)**	**N (%) (n=43)**
Number of respiratory disease-related hospitalisations						
0 1-2 ≥3	8189 (93.24) 577 (6.57) 17 (0.19)	447 (82.47) 90 (16.61) 5 (0.92)	2878 (88.99) 323 (9.99) 33 (1.02)	10 (66.67) 4 (26.67) 1 (6.67)	8694 (90.58) 867 (9.03) 37 (0.39)	24 (55.81) 10 (23.26) 9 (20.93)
Patients with at least 1 emergency room visit for COPD in the year before CED	2052 (23.36)	196 (36.16)	62 (1.92)	4 (26.67)	2046 (21.32)	40 (93.02)
Patients with at least 1 emergency room visit for COPD in the 30 days before CED	330 (3.76)	74 (13.65)	15 (0.46)	3 (20.00)	520 (5.42)	33 (76.74)
Prior use of oxygen	NA	NA	174 (5.38)	3 (20.00)	4335 (45.17)	38 (88.37)
Current use of theophylline at CED	1734 (19.74)	208 (38.38)	129 (3.99)	5 (33.33)	709 (7.39)	16 (37.21)
Current use of acetylcysteine at CED	710 (8.08)	138 (25.46)	1381 (42.70)	13 (86.67)	32 (0.33)	2 (4.65)
Charlson Comorbidity Index						
0-2 3-5 ≥6	4785 (54.48) 3057 (34.81) 941 (10.71)	305 (56.27) 180 (33.21) 57 (10.52)	2097 (64.84) 990 (30.61) 147 (4.55)	9 (60.00) 6 (40.00) 0 (0.00)	3210 (33.44) 3928 (40.93) 2460 (25.63)	14 (32.56) 22 (51.16) 7 (16.28)
Emphysema	3445 (39.22)	363 (66.97)	397 (12.28)	5 (33.33)	4670 (48.66)	39 (90.70)
Number of moderate COPD exacerbations[c]						
0 1-2 ≥3	1761 (20.05) 2583 (29.41) 4439 (50.54)	25 (4.61) 81 (14.94) 436 (80.44)	469 (14.50) 688 (21.27) 2077 (64.22)	NA NA 15 (100.00)	931 (9.70) 1865 (19.43) 6802 (70.87)	NA 2 (4.65) 41 (95.35)

Table 15 Age, Sex and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients

	GER		SWE		US	
	Exposed with matches	**Exposed without matches**	**Exposed with matches**	**Exposed without matches**	**Exposed with matches**	**Exposed without matches**
	N (%) (n=8783)	**N (%) (n=542)**	**N (%) (n=3234)**	**N (%) (n=15)**	**N (%) (n=9598)**	**N (%) (n=43)**
Treatment intensity score[d]						
0 1-2 3 4	424 (4.83) 1192 (13.57) 2415 (27.50) 4752 (54.10)	0 (0.00) 19 (3.51) 71 (13.10) 452 (83.39)	128 (3.96) 420 (12.99) 645 (19.94) 2041 (63.11)	0 (0.00) 0 (0.00) 2 (13.33) 13 (86.67)	1087 (11.33) 2339 (24.37) 2203 (22.95) 3969 (41.35)	NA 3 (6.98) 8 (18.60) 32 (74.42)
Chronic use of systemic corticosteroids	811 (9.23)	137 (25.28)	341 (10.54)	9 (60.00)	781 (8.14)	14 (32.56)
Propensity Score class counts[e]						
1	1755 (19.98)	0 (0.00)	NA	NA	1929 (20.10)	NA
2	1757 (20.00)	0 (0.00)	NA	NA	1928 (20.09)	NA
3	1758 (20.02)	0 (0.00)	NA	NA	1928 (20.09)	NA
4	1757 (20.00)	0 (0.00)	NA	NA	1928 (20.09)	NA
5	1756 (19.99)	542 (100.00)	NA	NA	1885 (19.64)	43 (100.00)

[a] p-values compare roflumilast-exposed matched and unmatched patients: Fisher's exact test for categorical variables and 2-sided t-test for continuous variables

[b] p-value obtained from test across categories: 0, 1, 2, ≥3

[c] In the US, moderate COPD exacerbations are defined in the following categories: 0, 1, ≥2, and chronic user (patient has a total days' supply >240 days/ 8 months during the 12 months prior to cohort entry).

[d] Treatment intensity score categories: 0=no COPD treatment; 1= SABA or SAMA only; 2=LABA or LAMA or ICS (±SAMA or SABA); 3=(LABA + LAMA) or (LABA + ICS) or (LAMA + ICS) (±SAMA or SABA); 4=LABA + LAMA + ICS (±SAMA or SABA).

[e] For the US, these quintiles are based on the matched study cohort of exposed and unexposed patients.

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; GER = Germany; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; max = maximum; min = minimum; N = number of patients per parameter; n = number of patients in overall population; NA = not available; Q1 = first quartile; Q3 = third quartile; SABA = short-acting β_2 agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation; SWE = Sweden; US = United States

Sources: Appendix 1 Table 3d, Table 5d; Appendix 2.1 Table 5; Appendix 3.1 Table 5

As might be expected in a group with higher COPD severity and despite the younger age, the crude MR in the roflumilast exposed unmatched patients was more than 70% and 50% higher than in the roflumilast exposed matched patients in GER and the US, respectively, while it was tripled in SWE (Table 16).

Table 16 Mortality Rates Per 1000 Person-years and Mortality Rate Ratio with 95% CIs in Matched and Unmatched Roflumilast-exposed Patients

	GER[a,b]		SWE		US	
	Matched	**Unmatched**	**Matched**	**Unmatched**	**Matched**	**Unmatched**
Deaths (person-years)	3230 (34453)	300 (1813)	1830 (14663)	13 (34)	5318 (40613)	28 (141)
N at risk	8775	542	3234	15	9,598	43
MR (95% CI)	93.75 (90.54, 97.04)	165.52 (147.32, 185.35)	124.80 (119.21, 130.65)	384.57 (223.30, 662.30)	130.94 (127.47, 134.51)	197.96 (136.68, 286.70)
Crude MRR (95% CI)	1 (ref)	1.77 (1.57, 1.99)	1 (ref)	3.08 (1.79, 5.32)	1 (ref)	1.51 (1.04, 2.19)

[a] 5-year all-cause mortality reported for GER.

[b] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

CI = confidence interval; GER = Germany; MR = mortality rates; MRR = mortality rate ratio; ref. = reference; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 10b; Appendix 2.1 Table 6; Appendix 3.1 Table 6

In addition, an analysis of time to death in roflumilast-exposed matched and unmatched patients was conducted. Survival percentages for the first 9 months were very similar in matched and unmatched patients, while the difference in MRs increase at about 1 year (Appendix 1, Figure 4n; Appendix 2, Figure 2; Appendix 3, Figure 2).

10.2 Descriptive Analyses

10.2.1 Number of Roflumilast Dispensations

The number of roflumilast dispensations for each annual cohort over the follow-up period and per country are described in Table 17. Approximately half the patients in GER and SWE and slightly less than half in the US had 1 to 3 dispensations. Approximately one third of patients in each country had 10 or more dispensations.

The proportion of patients with only 1 roflumilast dispensation was 31.5%, 32.9%, and 31.4% in GER, 26.0%, 25.6% and 27.2% in the US, and 31.3%, 33.4%, and 34.3% in SWE in the 2011, 2012, and 2013 cohorts, respectively.

Table 17 Roflumilast Dispensations by Calendar Year of Cohort Entry Including All Follow-up Time for the Respective Cohort

	2011			2012			2013		
	GER N (%)	SWE N (%)	US N (%)	GER N (%)	SWE N (%)	US N (%)	GER N (%)	SWE N (%)	US N (%)
Number of roflumilast-exposed patients									
Total	4958 (100.00)	1293 (100.00)	2220 (100.00)	2060 (100.00)	1210 (100.00)	4451 (100.00)	1757 (100.00)	731 (100.00)	2927 (100.00)
Number of roflumilast dispensations per patient									
0	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
1-3	2471 (49.84)	698 (53.98)	930 (41.90)	1066 (51.75)	661 (54.63)	1844 (41.43)	848 (48.26)	407 (55.69)	1283 (43.83)
1	1561 (31.48)	404 (31.25)	576 (25.95)	677 (32.86)	404 (33.39)	1138 (25.57)	551 (31.36)	251 (34.34)	797 (27.23)
2	601 (12.12)	209 (16.16)	220 (9.91)	269 (13.06)	170 (14.05)	438 (9.84)	197 (11.21)	114 (15.60)	300 (10.25)
3	309 (6.23)	85 (6.57)	134 (6.04)	120 (5.83)	87 (7.19)	268 (6.02)	100 (5.69)	42 (5.75)	186 (6.35)
4-6	481 (9.70)	167 (12.92)	254 (11.44)	227 (11.02)	127 (10.50)	506 (11.37)	191 (10.87)	58 (7.93)	314 (10.73)
7-9	332 (6.70)	68 (5.26)	159 (7.16)	139 (6.75)	61 (5.04)	295 (6.63)	120 (6.83)	41 (5.61)	191 (6.53)
10 or more	1674 (33.76)	360 (27.84)	877 (39.51)	628 (30.49)	361 (29.83)	1806 (40.58)	598 (34.04)	225 (30.78)	1139 (38.91)
Range (min, max)	(1, 83)	(1, 53)	(1, 125)	(1, 70)	(1, 63)	(1, 119)	(1, 67)	(1, 54)	(1, 129)
Mean (±SD)	9.47 (11.10)	8.22 (10.35)	13.58 (17.09)	8.35 (9.69)	8.31 (10.14)	13.64 (16.68)	8.25 (8.84)	7.90 (9.24)	12.85 (15.86)
Median (Q1, Q3)	4 (1, 15)	3 (1, 11)	5 (1, 19)	3 (1, 14)	3 (1, 13)	6 (1, 21)	4 (1, 14)	3 (1,13)	5 (1, 21)

Table 17 Roflumilast Dispensations by Calendar Year of Cohort Entry Including All Follow-up Time for the Respective Cohort

	2011			2012			2013		
	GER N (%)	**SWE N (%)**	**US N (%)**	**GER N (%)**	**SWE N (%)**	**US N (%)**	**GER N (%)**	**SWE N (%)**	**US N (%)**
Distribution of number of DDs dispensed per dispensation									
Range (min, max)	(24, 143)	(30, 270)	(1, 90)	(30, 117)[a]	(30, 360)	(1, 90)	(30, 150)	(30, 360)	(1, 90)
Mean (±SD)	65.02 (25.78)	76.88 (25.34)	62.25 (30.01)	62.33 (25.86)[a]	77.04 (25.85)	64.65 (29.75)	61.33 (25.51)	75.99 (26.76)	64.48 (29.82)
Median (Q1, Q3)	77 (30, 90)	90 (90, 90)	90 (30, 90)	70 (30, 90)	90 (90, 90)	90 (30, 90)	70 (30, 87)	90 (90, 90)	90 (30, 90)

[a] One outlier excluded

DD = daily dose; GER = Germany; max = maximum; min = minimum; N = number of patients in overall population; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 7 and Table 8c; Appendix 2.1 Table 7, Appendix 3.1 Table 7

In each country, mean and median number of dispensations decreased with the shortening of the follow-up time due to study entry in 2013. In GER, the mean±SD number of roflumilast dispensations decreased from 9.47±11.10 in the 2011 cohort to 8.25±8.84 in the 2013 cohort, compared with 8.22±10.35 to 7.90±9.24 in SWE, and 13.58±17.09 to 12.85±15.86 in the US, respectively.

Mean number of doses dispensed per dispensation appeared to remain stable over the cohorts and follow-up time. In GER, the mean±SD number of roflumilast dispensations was 65.02±25.78 in the 2011 cohort and 61.33±25.51 in the 2013 cohort, compared with 76.88±25.34 and 75.99±26.76 in SWE, and 62.25±30.01 and 66.00±29.68 in the US, respectively.

10.2.2 Descriptive Analyses Related to Follow-up

Within each country, the follow-up time was comparable in the roflumilast-exposed and unexposed patients. Similarly, no significant differences were noted across study countries (Table 18).

Table 18 Follow-up Time (Days) in Never and Ever Exposed to Roflumilast and the Total Population

	GER		SWE		US	
Statistic (days)	**Never exposed**	**Ever Exposed**	**Never exposed**	**Ever Exposed**	**Never exposed**	**Ever Exposed**
Range (min, max)	(1, 3061)	(2, 3074)	(1, 2920)	(1, 2913)	(1, 2779)	(1, 2779)
Mean (±SD)	1782.98 (922.47)	1804.23 (891.25)	1621.01 (901.58)	1656.09 (862.96)	1566.26 (850.10)	1545.51 (832.82)
Median	2020	2008	1895	1908	1877	1808
Q1	961	1057	759	885	760	772
Q3	2584	2573	2401	2388	2297	2276

GER = Germany; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SWE = Sweden; US = United States.
Sources: Appendix 1Table 9d; Appendix 2.1 Table 8, Appendix 3.1 Table 8

As described in Section 9.3.5, unexposed patients serving as controls who later became exposed to roflumilast were included upon switch into the roflumilast exposed cohort and thus could contribute person time to both the exposed and unexposed cohorts. Among the 41784, 15776, and 47151 unexposed patients in GER, SWE, and the US, respectively, 1402 (3.35%) in GER, 608 (3.85%) patients in SWE, and 1637 (3.47%) in the US, were exposed to roflumilast in a later annual cohort after study entry and switched to the exposed cohort. These switchers were counted twice in the analyses in this report (but their follow-up time was counted separately as exposed or unexposed, as previously described).

10.3 Outcomes - Descriptive Statistics

10.3.1 Primary Outcome of 5-year All-cause Mortality

The number of 5-year all-cause mortality events and person-years of follow-up for the roflumilast-exposed and unexposed cohorts per country are shown in Table 19.

Table 19 5-year All-cause Mortality Events in Ever-Versus-Never Users of Roflumilast

5-year all-cause mortality	Ever use (exposed) N of events (PY)	Never use (unexposed) N of events (PY)
GER	3230 (34453)	12071 (160716)
SWE	1475 (12139)	6104 (57594)
US	4590 (34779)	17539 (171688)

GER = Germany; PY = person-years; SWE = Sweden; US = United States.
Sources: Appendix 1 Table 10a; Appendix 2.1 Table 9; Appendix 3.1 Table 9

Cause of death data are only available for SWE. Table 20 lists the most frequent causes of death in SWE by use status of roflumilast at the time of death (current, recent, past) and never use. The most frequent cause of death in SWE was COPD, accounting for 52.8% of deaths in the unexposed cohort and for 54.6%, 54.4% and 51.9% of deaths in the exposed cohort during current, recent, and past exposure, respectively. The proportion of patients in the exposed cohort for each of the other causes of death was slightly lower than or equivalent to the unexposed group.

Table 20 Frequency Distribution of Cause of Death by Exposure Status in SWE

Cause of death	Never use (unexposed) N of events (%)	Ever use (exposed) N of events (%)	Current use (exposed) N of events (%)	Recent use (exposed) N of events (%)	Past use (exposed) N of events (%)
Ischaemic heart disease (I20-I25)	709 (9.72)	140 (7.65)	45 (7.68)	8 (11.76)	87 (7.40)
Heart failure (I50)	216 (2.96)	34 (1.86)	13 (2.22)	1 (1.47)	20 (1.70)
Cardiomyopathy (I42, I44, I45)	20 (0.27)	2 (0.11)	1 (0.17)	NA	1 (0.09)
Cerebrovascular disease (I60-I69)	168 (2.30)	23 (1.26)	3 (0.51)	NA	20 (1.70)

Table 20 Frequency Distribution of Cause of Death by Exposure Status in SWE

Cause of death	Never use (unexposed) N of events (%)	Ever use (exposed) N of events (%)	Current use (exposed) N of events (%)	Recent use (exposed) N of events (%)	Past use (exposed) N of events (%)
COPD (J44)	3110 (42.62)	967 (52.84)	320 (54.61)	37 (54.41)	610 (51.87)
Lung Cancer (C34)	512 (7.02)	119 (6.50)	37 (6.31)	5 (7.35)	77 (6.55)
Influenza and/or pneumonia (J09-J18)	78 (1.07)	17 (0.93)	5 (0.85)	NA	12 (1.02)
Other acute lower respiratory infections (J20-J22)	1 (0.01)	NA	NA	NA	NA
Other interstitial pulmonary disease (J84)	59 (0.81)	9 (0.49)	4 (0.68)	NA	5 (0.43)
Cancer (other than lung cancer) (C00-C97, except C34, C44)	1153 (15.80)	237 (12.95)	67 (11.43)	8 (11.76)	162 (13.78)
Other causes	1783 (24.43)	401 (21.91)	128 (21.84)	14 (20.59)	259 (22.02)
All-cause mortality	**7297**	**1830**	**586**	**68**	**1176**

COPD = chronic obstructive pulmonary disease; SWE = Sweden
Source: Appendix 2.1 Table 10

10.3.2 Secondary Outcomes

The number of events per secondary outcomes (except cancer) are provided for current, recent, past, and never use of roflumilast, together with PYs at risk and the crude IRs with 95% CIs for GER, SWE and the US in Table 21, Table 22 and Table 23, respectively. The numbers of cancer-related events for ever roflumilast exposure compared to never exposure are shown in Table 24.

In all countries, hospitalisation for any cause and respiratory disease-related hospitalisation were the most frequent secondary outcomes. The crude IRs of respiratory disease-related hospitalisation in current and recent users compared to never users were more than twofold elevated in GER and SWE and similarly almost twofold elevated in the US, possibly related to the higher COPD severity in the exposed patients. Crude IRs of major cardiovascular events were similar in current and never users in GER, SWE and the US (Table 21 for GER, Table 22 for SWE, and Table 23 for the US). Crude IRs in current and never users varied substantially between countries (eg, for new diagnosis of depression, abnormal unexplained weight loss).

Table 21 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in GER

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
Hospitalisation for any cause	4830 (6524)	740.30 (719.57, 761.48)	574 (759)	756.39 (695.77, 820.88)	2725 (5965)	456.80 (439.81, 474.28)	36299 (76877)	472.17 (467.33, 477.05)
Respiratory disease-related hospitalisation	3079 (11077)	277.96 (268.23, 287.96)	333 (1120)	297.41 (266.32, 331.13)	2276 (13414)	169.68 (162.78, 176.80)	19413 (154396)	125.74 (123.97, 127.52)
Major cardiovascular events[a]	702 (16988)	41.32 (38.32, 44.50)	78 (1518)	51.39 (40.62, 64.13)	909 (21293)	42.69 (39.96, 45.56)	7503 (187842)	39.94 (39.04, 40.86)
Arrhythmia[b]	16 (18070)	8.85 (5.06, 14.38)	2 (1602)	12.49 (1.51, 45.11)	38 (23542)	16.14 (11.42, 22.15)	321 (202855)	15.82 (14.14, 17.65)
Myocardial infarction	164 (17814)	9.21 (7.85, 10.73)	19 (1582)	12.01 (7.23, 18.75)	228 (23044)	9.89 (8.65, 11.27)	1823 (199700)	9.13 (8.71, 9.56)
Cerebral infarction	101 (17932)	5.63 (4.59, 6.84)	12 (1592)	7.54 (3.89, 13.16)	173 (23194)	7.46 (6.39, 8.66)	1442 (200350)	7.20 (6.83, 7.58)
Heart failure	429 (17494)	24.52 (22.26, 26.96)	46 (1556)	29.57 (21.65, 39.44)	476 (22542)	21.12 (19.26, 23.10)	4166 (195987)	21.26 (20.62, 21.91)
Pulmonary embolism[b]	53 (18002)	29.44 (22.05, 38.51)	7 (1598)	43.79 (17.61, 90.23)	113 (23346)	48.40 (39.89, 58.19)	718 (202168)	35.52 (32.96, 38.21)
Hospitalisation due to diarrhoea of non-infectious origin[b]	27 (18036)	14.97 (9.87, 21.78)	4 (1600)	24.99 (6.81, 63.99)	31 (23546)	13.17 (8.95, 18.69)	271 (202939)	13.35 (11.81, 15.04)
Abnormal, unexplained weight loss[b]	29 (18040)	16.08 (10.77, 23.09)	0 (1599)	0.00 (0.00, 23.07)	15 (23565)	6.37 (3.56, 10.50)	130 (202838)	6.41 (5.35, 7.61)
New diagnosis of depression	114 (17401)	6.55 (5.40, 7.87)	14 (1541)	9.09 (4.97, 15.25)	106 (22562)	4.70 (3.85, 5.68)	670 (190342)	3.52 (3.26, 3.80)
Hospitalisation for suicide attempt[b]	30 (18022)	16.65 (11.23, 23.76)	4 (1596)	25.06 (6.83, 64.17)	43 (23516)	18.29 (13.23, 24.63)	255 (202522)	12.59 (11.09, 14.24)

Table 21 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in GER

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
New diagnosis of tuberculosis, hepatitis B or C or other severe viral hepatitis infection (except hepatitis A)[b]	4 (17984)	2.22 (0.61, 5.69)	2 (1592)	12.56 (1.52, 45.38)	1 (23445)	0.43 (0.01, 2.38)	38 (200197)	1.90 (1.34, 2.61)

[a] Only first event was counted in the composite outcome.

[b] Incidence rate is per 10,000 PY for arrhythmia, pulmonary embolism, diarrhoea, weight loss, suicide and tuberculosis/hepatitis. All other outcomes were per 1000 PY.

CI = confidence interval; GER = Germany; PY = person-years

Source: Appendix 1 Table 13.a1, Table 14, Table 15, Table 16, Table 17, Table 18, Table 19, Table 20, Table 21, Table 22, Table 24, Table 25, Table 26

Table 22 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in SWE

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
Hospitalisation for any cause	1699 (2689)	631.60 (602.27, 662.36)	185 (271)	682.37 (590.79, 788.13)	1015 (2561)	396.21 (372.57, 421.35)	13,008 (32173)	404.31 (397.43, 411.32)
Respiratory disease-related hospitalisation	1271 (3666)	346.64 (328.10, 366.23)	147 (339)	432.77 (368.18, 508.71)	883 (4264)	207.05 (193.83, 221.17)	8416 (50177)	167.73 (164.18, 171.35)
Major cardiovascular events	229 (5520)	41.48 (36.44, 47.21)	35 (486)	72.02 (51.71, 100.30)	360 (7355)	48.94 (44.14, 54.27)	2901 (64251)	45.15 (43.54, 46.82)
Arrhythmia	11 (5847)	18.81 (10.42, 33.97)	2 (510)	39.15 (9.79, 156.55)	14 (8245)	16.98 (10.06, 28.67)	131 (69722)	18.79 (15.83, 22.30)
Myocardial infarction	59 (5779)	10.21 (7.91, 13.18)	8 (504)	15.86 (7.93, 31.72)	107 (8002)	13.37 (11.06, 16.16)	801 (68286)	11.73 (10.95, 12.57)

Table 22 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in SWE

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
Cerebral infarction	33 (5810)	5.68 (4.04, 7.99)	7 (507)	13.80 (6.58, 28.94)	56 (8097)	6.92 (5.32, 8.99)	551 (68846)	8.00 (7.36, 8.70)
Heart failure	117 (5719)	20.46 (17.07, 24.52)	14 (502)	27.87 (16.51, 47.06)	168 (7926)	21.19 (18.22, 24.65)	1,383 (67774)	20.41 (19.36, 21.51)
Pulmonary embolism	29 (5820)	49.82 (34.62, 71.70)	5 (507)	98.44 (40.97, 236.51)	74 (8102)	91.33 (72.72, 114.70)	421 (69196)	60.84 (55.30, 66.94)
Hospitalisation due to diarrhoea of non-infectious origin	37 (5819)	63.58 (46.07, 87.75)	4 (508)	78.68 (29.53, 209.63)	31 (8180)	37.89 (26.65, 53.88)	250 (69517)	35.96 (31.77, 40.71)
Abnormal, unexplained weight loss	14 (5842)	23.96 (14.19, 40.45)	3 (509)	58.83 (18.98, 182.42)	17 (8224)	20.67 (12.85, 33.25)	107 (69614)	15.37 (12.72, 18.58)
New diagnosis of depression	5 (5809)	0.86 (0.36, 2.07)	0 (507)	NC	5 (8182)	0.61 (0.25, 1.47)	34 (68703)	0.49 (0.35, 0.69)
Hospitalisation for suicide attempt	7 (5737)	12.20 (5.82, 25.59)	0 (502)	NC	12 (8146)	14.73 (8.37, 25.94)	92 (67387)	13.65 (11.13, 16.75)
New diagnosis of tuberculosis, hepatitis B or C or other severe viral hepatitis infection (except hepatitis A)	5 (5821)	8.59 (3.58, 20.64)	0 (507)	NC	2 (8180)	2.44 (0.61, 9.78)	35 (68489)	5.11 (3.67, 7.12)

CI = confidence interval; NC = not calculated; PY = person-years; SWE = Sweden
Incidence rate is per 1000 PY
Source: Appendix 2.1 Table 11

Table 23 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in the US

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
Hospitalisation for any cause	4539 (9796)	463.31 (450.03, 476.99)	525 (965)	543.96 (499.36, 592.54)	2768 (8357)	331.19 (319.07, 343.76)	36001 (105390)	341.60 (338.09, 345.14)
Respiratory disease-related hospitalisation	2755 (13262)	207.74 (200.12, 215.64)	336 (1218)	275.86 (247.89, 306.99)	1948 (13425)	145.09 (138.79, 151.68)	18902 (159129)	118.78 (117.10, 120.49)
Major cardiovascular events	599 (17716)	33.81 (31.21, 36.63)	80 (1540)	51.92 (41.70, 64.64)	577 (18943)	30.46 (28.07, 33.05)	6262 (189628)	33.02 (32.21, 33.85)
Arrhythmia	7 (18579)	3.77 (1.80, 7.90)	0 (1609)	NC	6 (20408)	2.94 (1.32, 6.54)	100 (202056)	4.95 (4.07, 6.02)
Myocardial infarction	160 (18337)	8.73 (7.47, 10.19)	19 (1591)	11.94 (7.61, 18.71)	171 (19999)	8.55 (7.36, 9.93)	1619 (198855)	8.14 (7.75, 8.55)
Cerebral infarction	127 (18356)	6.92 (5.81, 8.23)	16 (1592)	10.05 (6.15, 16.40)	131 (20014)	6.55 (5.52, 7.77)	1426 (198938)	7.17 (6.81, 7.55)
Heart failure	298 (18202)	16.37 (14.61, 18.34)	45 (1575)	28.55 (21.32, 38.24)	269 (19835)	13.56 (12.03, 15.28)	3006 (196859)	15.27 (14.73, 15.83)
Pulmonary embolism	43 (18535)	23.20 (17.20, 31.28)	6 (1605)	37.37 (16.79, 83.19)	68 (20245)	33.59 (26.48, 42.60)	580 (201040)	28.85 (26.60, 31.30)
Hospitalisation due to diarrhoea of non-infectious origin	245 (18065)	135.61 (119.65, 153.70)	27 (1568)	172.14 (118.05, 251.01)	179 (19715)	90.79 (78.42, 105.12)	1878 (197389)	95.14 (90.93, 99.54)
Abnormal, unexplained weight loss	1441 (15655)	920.44 (874.12, 969.21)	99 (1406)	703.94 (578.08, 857.21)	777 (16953)	458.31 (427.19, 491.70)	8519 (177331)	480.40 (470.31, 490.71)
New diagnosis of depression	720 (7176)	100.33 (93.26, 107.93)	83 (636)	130.50 (105.24, 161.82)	622 (7787)	79.87 (73.83, 86.40)	3277 (46697)	70.17 (67.81, 72.62)

Table 23 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in the US

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)	N of events (PY)	Incidence rate (95% CI)
Hospitalisation for suicide attempt	52 (18429)	28.22 (21.50, 37.03)	4 (1593)	25.10 (9.42, 66.87)	56 (20190)	27.74 (21.35, 36.04)	564 (199304)	28.30 (26.06, 30.73)
New diagnosis of tuberculosis, hepatitis B or C or other severe viral hepatitis infection (except hepatitis A)	59 (18227)	32.37 (25.08, 41.78)	10 (1574)	63.52 (34.18, 118.06)	67 (19864)	33.73 (26.55, 42.85)	612 (194046)	31.54 (29.14, 34.14)

Incidence rate is per 10,000 PY for arrhythmia, pulmonary embolism, diarrhoea, weight loss, suicide and hepatitis. All other outcomes were per 1000 PY.

CI = confidence interval; PY = person-years; US = United States

Source: Appendix 3.1 Table 11

As previously reported in the interim reports for the outcome malignant neoplasms, in all countries crude IR estimates were higher in the exposed compared with the unexposed cohorts. The crude IRs in never users were similar in GER and the US, but higher in SWE. This could be related to different ascertainment of cancers which was based on a cancer registry in SWE, but only on ICD codes in GER and the US. Furthermore, the greatest IR estimates were observed when no latency period was applied (Table 24). Reductions were modest in GER, SWE, and the US when comparing estimates with no latency to estimates with 1 and 2 years latency. In all countries haematopoietic tumours accounted for less than 10% of all malignant neoplasms.

Table 24 Number of Malignant Events, Number of Patients at Risk, and Incidence Rates for Ever-Versus-Never Use of Roflumilast

	GER				SWE				US			
Outcomes	Exposed N events (N at risk)	Unexposed N events (N at risk)	Exposed IR (95% CI)	Unexposed IR (95% CI)	Exposed N events (N at risk)	Unexposed N events (N at risk)	Exposed IR (95% CI)	Unexposed IR (95% CI)	Exposed N events (N at risk)	Unexposed N events (N at risk)	Exposed IR (95% CI)	Unexposed IR (95% CI)
Malignant neoplasms[a]												
No latency (new diagnosis)	1088 (7419)	3688 (30061)	306.72 (288.76, 325.50)	253.52 (245.40, 261.83)	405 (2690)	1410 (11011)	347.23 (315.01, 382.75)	295.80 (280.75, 311.65)	1077 (9063)	4531 (41420)	287.00 (270.36, 304.66)	257.11 (249.73, 264.70)
No latency (follow-up limit to 1 year)	198 (7419)	716 (30061)	281.93 (244.02, 324.05)	251.85 (233.73, 270.99)	90 (2690)	302 (11011)	358.23 (291.37, 440.44)	296.87 (265.20, 332.31)	256 (9063)	1137 (41420)	303.70 (268.69, 343.28)	295.61 (278.92, 313.30)
1 year latency	844 (6444)	2491 (23473)	306.16 (285.85, 327.53)	240.80 (231.44, 250.45)	313 (2342)	971 (8390)	343.64 (307.61, 383.90)	288.11 (270.55, 306.81)	818 (7810)	2958 (31164)	281.85 (263.18, 301.84)	242.78 (234.19, 251.69)
2 years latency	625 (5601)	1672 (18579)	300.32 (277.24, 324.82)	231.99 (221.00, 243.38)	234 (1998)	679 (6478)	343.43 (302.13, 390.37)	294.54 (273.20, 317.55)	595 (6699)	1925 (24074)	276.45 (255.11, 299.58)	233.94 (223.72, 244.63)
Malignant neoplasms - solid tumours												
No latency (new diagnosis)	1055 (7484)	3598 (30657)	294.61 (277.10, 312.94)	242.69 (234.82, 250.75)	391 (2690)	1338 (11011)	334.24 (302.70, 369.07)	279.87 (265.27, 295.28)	1013 (9063)	4146 (41420)	269.13 (253.05, 286.22)	234.39 (227.36, 241.63)
No latency (follow-up limit to 1 year)	192 (7484)	711 (30657)	270.98 (234.01, 312.14)	245.34 (227.63, 264.05)	85 (2690)	287 (11011)	337.88 (273.17, 417.91)	281.97 (251.16, 316.55)	243 (9063)	1037 (41420)	288.12 (254.08, 326.72)	269.32 (253.42, 286.23)
1 year latency	822 (6514)	2439 (23996)	294.74 (274.93, 315.59)	230.62 (221.55, 239.96)	304 (2345)	921 (8411)	332.66 (297.29, 372.24)	271.96 (254.95, 290.11)	768 (7817)	2707 (31251)	263.67 (245.67, 283.00)	221.03 (212.86, 229.51)

Table 24 Number of Malignant Events, Number of Patients at Risk, and Incidence Rates for Ever-Versus-Never Use of Roflumilast

	GER				SWE				US			
Outcomes	**Exposed N events (N at risk)**	**Unexposed N events (N at risk)**	**Exposed IR (95% CI)**	**Unexposed IR (95% CI)**	**Exposed N events (N at risk)**	**Unexposed N events (N at risk)**	**Exposed IR (95% CI)**	**Unexposed IR (95% CI)**	**Exposed N events (N at risk)**	**Unexposed N events (N at risk)**	**Exposed IR (95% CI)**	**Unexposed IR (95% CI)**
2 years latency	611 (5672)	1653 (19038)	289.71 (267.20, 313.63)	223.73 (213.07, 234.78)	228 (2003)	642 (6504)	333.37 (292.79, 379.58)	276.84 (256.24, 299.11)	565 (6716)	1764 (24211)	261.44 (240.75, 283.92)	212.73 (203.03, 222.89)
Malignant neoplasms - haematopoietic / haematological tumours												
No latency (new diagnosis)	73 (8687)	316 (40739)	17.03 (13.35, 21.41)	15.88 (14.17, 17.73)	18 (2690)	90 (11011)	14.52 (9.15, 23.05)	17.93 (14.58, 22.04)	76 (9063)	479 (41420)	19.54 (15.61, 24.47)	26.32 (24.06, 28.78)
No latency (follow-up limit to 1 year)	14 (8687)	48 (40739)	16.92 (9.25, 28.39)	12.46 (9.19, 16.52)	6 (2690)	16 (11011)	23.58 (10.59, 52.49)	15.56 (9.53, 25.40)	17 (9063)	113 (41420)	19.97 (12.42, 32.13)	29.10 (24.20, 35.00)
1 year latency	54 (7802)	224 (33316)	15.76 (11.84, 20.57)	15.17 (13.25, 17.29)	12 (2404)	66 (8759)	12.23 (6.95, 21.54)	17.99 (14.13, 22.89)	58 (7955)	331 (32278)	19.14 (14.80, 24.76)	25.69 (23.07, 28.61)
2 years latency	37 (7022)	166 (27362)	13.91 (9.79, 19.17)	15.62 (13.33, 18.18)	7 (2096)	48 (7035)	9.40 (4.48, 19.71)	18.51 (13.95, 24.56)	38 (6916)	221 (25450)	16.77 (12.21, 23.05)	25.04 (21.95, 28.57)

[a] Patients with any neoplasm prior to CED excluded from analysis. Patients with any cancer event during the latency periods excluded in latency analyses.

Crude rate is per 1000 PY

Note: Subgroup analyses according to tumour subtype in GER excluded only patients with a prior diagnosis of the respective tumour subtype from N at risk.

CED = cohort entry date; CI = confidence interval; GER = Germany; PY = person-years; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 23 a1, Table 23 a2, Table 23 a3, Table 23 a4, Table 23 b1, Table 23 b2, Table 23 b3, Table 23 b4, Table 23 c1, Table 23 c2, Table 23 c3, Table 23 c4; Appendix 2.1 Table 12; Appendix 3.1 Table 12

Table 25 shows the extent to which the different diagnosis sub-classes (influenza, pneumonia and other acute lower respiratory infections, bronchitis, emphysema, COPD, asthma, bronchiectasis) contribute to the combined outcome respiratory disease-related hospitalisation. In GER, COPD accounted for 81.4% and 74.3% hospitalisations in the exposed and unexposed patients, respectively. A similar percentage of COPD-related hospitalisations in the exposed and unexposed were observed in SWE, where COPD was the cause of 78.8% hospitalisations in the exposed and 67.0% hospitalisations in the unexposed cohorts. A lower proportion of hospitalisation due to COPD overall was observed in the US with 54.3% of cases in the exposed and 46.5% in the unexposed, yet.

Table 25 Distribution of Causes of Respiratory Disease-related Hospitalisation Outcome

Diagnosis	Code	Country	Unexposed		Exposed		Total	
			N	%	N	%	N	%
Influenza, pneumonia, other acute lower respiratory infections	J09-J22	GER	4709	21.01	821	14.43	4900	19.52
	J09-J22	SWE	2554	30.35	457	19.86	3011	28.10
	ICD-10: J09-J22;ICD-9: 466, 480-483, 485-488, 514,4841, 4843, 4845-4848	US	5586	29.55	1112	22.07	6698	27.98
	J18+J44	GER[a]	7	0.04	1	0.02	8	0.03
	J20+J44	GER[a]	1	0.01	0	0	1	0.00
Bronchitis, not specified as acute or chronic; Simple and mucopurulent chronic bronchitis; Unspecified chronic bronchitis	J40-J42	GER	146	0.75	27	0.47	173	0.69
	J40+J44	GER[b]	1	0.01	0	0	1	0.00
	J40-J42	SWE	29	0.34	4	0.17	33	0.31
	ICD-10: J40-J42; ICD-9: 490	US	33	0.17	1	0.02	34	0.14
Emphysema	J43	GER	164	0.84	62	1.09	226	0.9
	J43	SWE	33	0.39	9	0.39	42	0.39
	ICD-10: J43; ICD-9: 492	US	71	0.38	29	0.58	100	0.42
COPD	J44	GER	14430	74.33	4629	81.38	19059	75.9
	J44	SWE	5640	67.02	1814	78.84	7454	69.55
	ICD-10: J44; ICD-9: 491, 496	US	8788	46.49	2738	54.34	11526	48.14
Asthma; Status asthmaticus	J45-J46	GER	468	2.41	117	2.06	585	2.33
	J45-J46	SWE	128	1.52	10	0.43	138	1.29
	ICD-10: J45-J46; ICD-9: 493	US	1102	5.83	284	5.64	1,386	5.79
Bronchiectasis	J47	GER	117	0.55	31	0.60	148	0.59
	J47	SWE	32	0.38	7	0.30	39	0.36

Table 25 Distribution of Causes of Respiratory Disease-related Hospitalisation Outcome

Diagnosis	Code	Country	Unexposed		Exposed		Total	
			N	%	N	%	N	%
	ICD-10: J47; ICD-9: 494	US	98	0.52	31	0.62	129	0.54
Other[c]	ICD-9: 460-465, 470-478, 500-513, 515, 519, 495	US	3224	17.06	844	16.75	4068	16.99
Total	-	GER	19413	100	5688	100	25101	100
		SWE	8416	100	2301	100	10717	100
		US	18902	100	5039	100	23941	100

[a] In GER a diagnosis of influenza, pneumonia, other acute lower respiratory infections were additionally based on the combination of codes J18+J44 and J20+J44

[b] In GER a diagnosis of bronchitis, not specified as acute or chronic; simple and mucopurulent chronic bronchitis; or unspecified chronic bronchitis were additionally based on the combination of codes J40+J44.

[c] ICD-9 diagnostic codes, listed in Appendix 1, Table 1 of the SAP and used to define respiratory disease that do not directly map to ICD-10 diagnostic codes are captured in the "Other" category.

COPD = chronic obstructive pulmonary disease; GER = Germany; ICD = International Classification of Diseases and Related Health Problems; SAP = statistical analysis plan; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 29; Appendix 2.1 Table 13; Appendix 3.1 Table 13

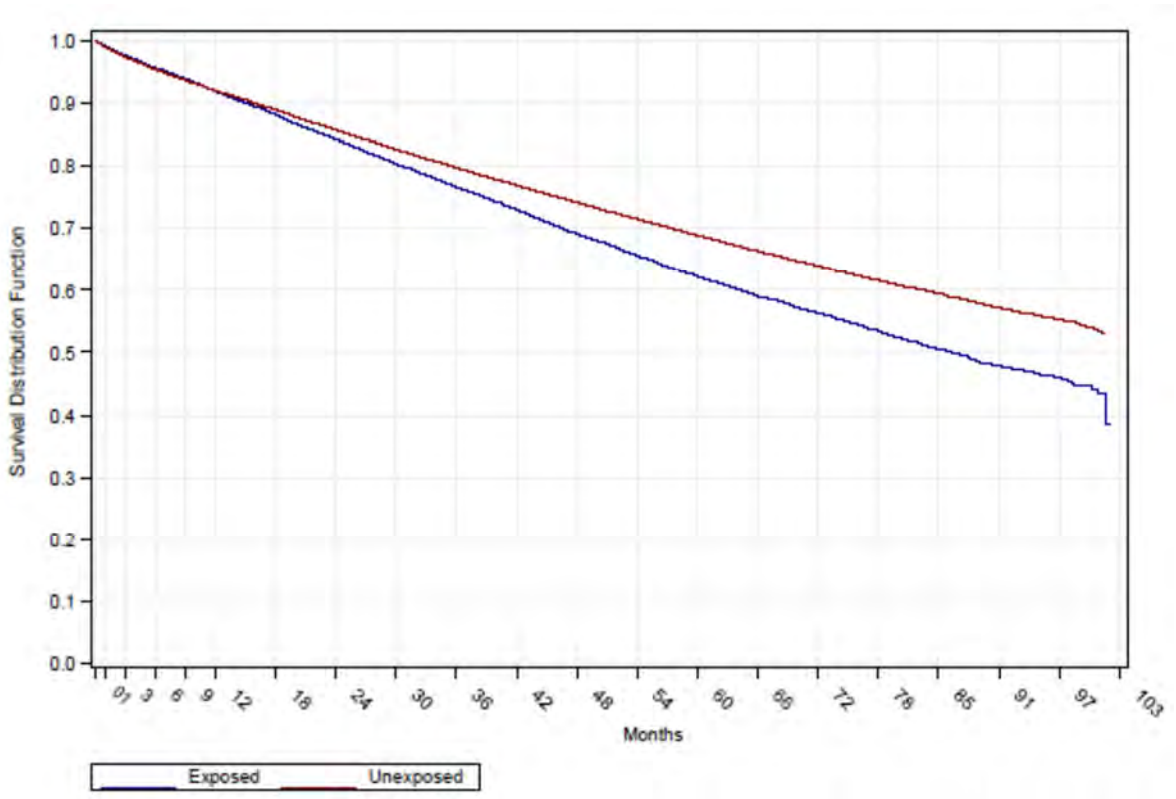
10.4 Outcomes - Main Results

10.4.1 Primary Outcome of 5-year All-cause Mortality

10.4.1.1 Kaplan-Meier Analyses

Kaplan-Meier estimates for 5-year all-cause mortality were calculated for overall survival in the ever and never exposed cohorts PS matched at study entry and without any further adjustments applied (Figure 11 for GER, Figure 12 for SWE, and Figure 13 for the US). These results showed that after approximately 9 months of follow up in the US and 1.5 years follow up in GER and SWE, the mortality risk was consistently higher in the roflumilast-exposed cohort compared to the unexposed cohort. After this point, an increasing separation of the survival curves was observed with higher mortality in the ever compared to the never-exposed cohort.

Figure 11 Survival Curves of All-cause Mortality in Never (Unexposed) and Ever (Exposed) Users of Roflumilast in GER



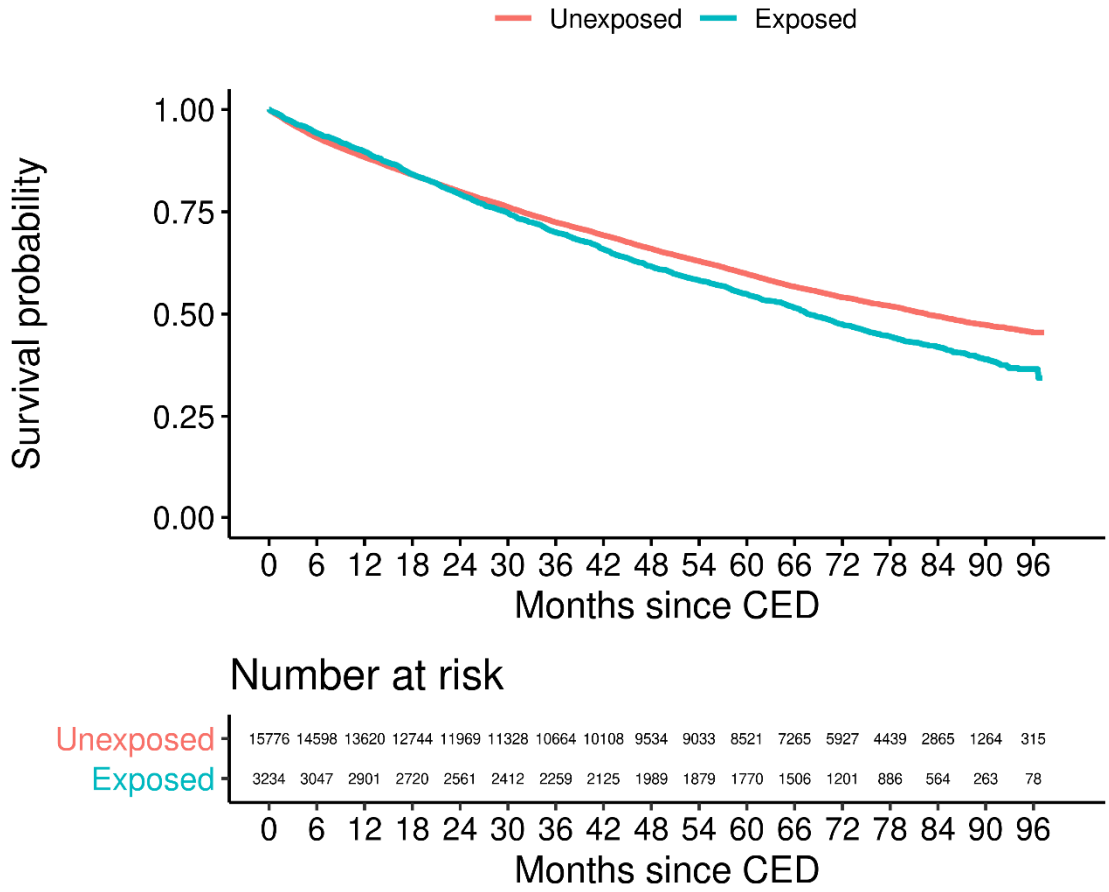
Number at Risk

Exposed																			
8775	8688	8542	8347	8179	7985	7624	7245	6864	6512	6158	5790	5447	5126	4384	3658	2953	2244	1504	571
Unexposed																			
41718	41249	40469	39461	38400	37364	35382	33483	31720	30063	28491	27042	25607	24267	20921	17436	14282	11051	7442	2784
1	**3**	**6**	**9**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**	**90**	**96**	**102**

Months Since CED

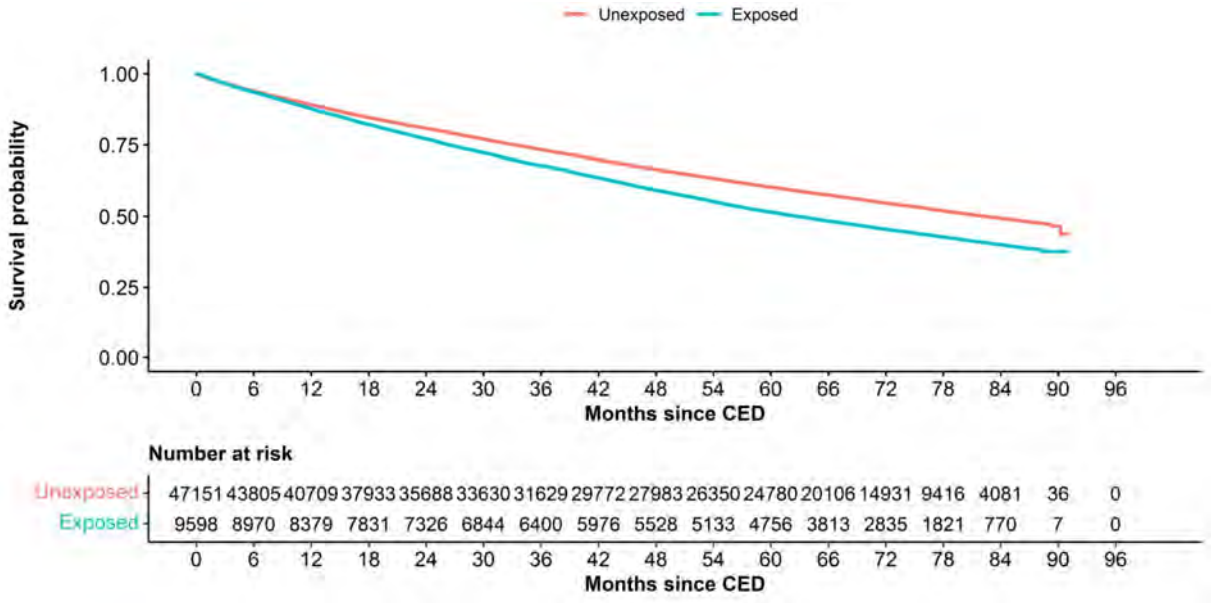
GER = Germany
Source: Appendix 1 Figure 4h, Table 12b1

Figure 12 Survival Curves of All-cause Mortality in Never (Unexposed) and Ever (Exposed) Users of Roflumilast in SWE



CED = cohort entry date; SWE = Sweden.

Figure 13 Survival Curves of All-cause Mortality in Never (Unexposed) and Ever (Exposed) Users of Roflumilast in the US



CED = cohort entry date; US = United States.

10.4.1.2 Crude Mortality Rates and Crude Mortality Rate Ratios by Different Exposure Categories for Roflumilast Exposure Versus No Exposure

Stratified crude MR and MRRs by exposure categories are presented in Table 26, Table 27, and Table 28, for GER, SWE, and the US, respectively. An elevated crude risk of death was observed for ever-versus-never use in GER (crude MRR of 1.25, 95% CI: 1.20, 1.30), in SWE (crude MRR of 1.15, 95% CI: 1.08, 1.21), and in the US (crude MRR of 1.29, 95% CI: 1.25, 1.33). In GER, the highest crude MRR was associated with a cumulative duration between 3 to 12 months, while in SWE and the US the highest MRRs were observed for the shortest cumulative duration of roflumilast exposure (up to 3 months), and the longest cumulative duration of roflumilast exposure (more than 12 months) was associated with the lowest risk estimates.

For roflumilast exposure classified by exposure status at the time of the outcome events (ie, current, recent, and past versus never use), the least elevated MRRs were seen for current use; in SWE there was no risk increase for current users.

Stratification of crude estimates of mortality by time since discontinuation did not show a consistent pattern across countries. In line with the observed higher MRRs during recent use, crude estimates of risk in the days 1 to 89 after discontinuation was particularly elevated in GER and the US. The MRR level for 3 to 12 months and for more than 12 months was similar in all countries.

Table 26 5-Year All-cause MRs and Crude MRRs for Different Exposure Definitions of Roflumilast Exposure Versus No Exposure in GER

	N at risk[a]	PY	No of events	Crude MR/1000 PY (95% CI)	Crude MRR (95% CI)
Ever use					
Never	41718	160716	12071	75.11 (73.77, 76.46)	1 (ref.)
Ever	8775	34453	3230	93.75 (90.54, 97.04)	1.25 (1.20, 1.30)
Cumulative duration					
Up to 3 months	8775	11916	1053	88.37 (83.11, 93.87)	1.18 (1.10, 1.25)
3 to 12 months	6154	11457	1129	98.54 (92.88, 104.46)	1.31 (1.23, 1.39)
More than 12 months	3642	11081	1048	94.58 (88.94, 100.48)	1.26 (1.18, 1.34)
Use status					
Current	8775	15183	1242	81.80 (77.32, 86.48)	1.09 (1.03, 1.15)
Recent	7255	1481	201	135.73 (117.61, 155.84)	1.81 (1.57, 2.08)
Past	6305	17790	1787	100.45 (95.85, 105.22)	1.34 (1.27, 1.41)
Time since discontinuation					
Concurrent	8775	15010	1219	81.22 (76.72, 85.91)	1.08 (1.02, 1.15)
Up to 3 months (1-89 days)	7397	2265	288	127.14 (112.88, 142.71)	1.69 (1.51, 1.90)
3 to 12 months	6044	4544	470	103.42 (94.28, 113.21)	1.38 (1.26, 1.51)
More than 12 months	4909	12634	1253	99.18 (93.76, 104.82)	1.32 (1.25, 1.40)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

CI = confidence interval; GER = Germany; MR = mortality rate; MRR = mortality rate ratio; N = number of patients; ref. = reference; PY = person-years.

Source: Appendix 1 Table 11a1.1

Table 27 5-Year All-cause MRs and Crude MRRs for Different Exposure Definitions of Roflumilast Exposure Versus No Exposure in SWE

	N at risk	PY	No of events	Crude MR/1000 PY (95% CI)	Crude MRR (95% CI)
Ever use					
Never	15776	57594	6,104	105.98 (103.36, 108.68)	1 (ref.)
Ever	3234	12139	1,475	121.51 (115.46, 127.87)	1.15 (1.08, 1.21)
Cumulative duration					
Up to 3 months	3234	3827	503	131.42 (120.42, 143.42)	1.24 (1.13, 1.36)
3 to 12 months	2310	4686	586	125.03 (115.31, 135.57)	1.18 (1.08, 1.28)
More than 12 months	1171	3624	386	106.49 (96.38, 117.66)	1.00 (0.91, 1.11)
Use status					
Current	3234	5078	506	99.63 (91.31, 108.70)	0.94 (0.86, 1.03)
Recent	2520	484	62	127.93 (99.74, 164.08)	1.21 (0.94, 1.55)
Past	2305	6575	907	137.93 (129.24, 147.21)	1.30 (1.21, 1.40)

Table 27 5-Year All-cause MRs and Crude MRRs for Different Exposure Definitions of Roflumilast Exposure Versus No Exposure in SWE

	N at risk	PY	No of events	Crude MR/1000 PY (95% CI)	Crude MRR (95% CI)
Time since discontinuation					
Concurrent	3234	5025	496	98.70 (90.38, 107.78)	0.93 (0.85, 1.02)
Up to 3 months (1-89 days)	2582	764	106	138.60 (114.57, 167.66)	1.31 (1.08, 1.58)
3 to 12 months	2232	1670	216	129.27 (113.13, 147.71)	1.22 (1.06, 1.40)
More than 12 months	1869	4677	657	140.45 (130.11, 151.61)	1.33 (1.22, 1.44)

CI = confidence interval; MR = mortality rate; MRR = mortality rate ratio; PY = person-years; ref. = reference; SWE = Sweden

Source: Appendix 2.1 Table 14

Table 28 Crude 5-Year All-cause MR and Crude MRRs for Different Exposure Definitions of Roflumilast Exposure Versus No Exposure in the US

	N at risk	PY	No of events	Crude MR/1000 PY (95% CI)	Crude MRR (95% CI)
Ever use					
Never	47151	171688	17539	102.16 (100.66, 103.68)	Reference
Ever	9598	34779	4590	131.97 (128.21, 135.85)	1.29 (1.25, 1.33)
Cumulative duration					
Up to 3 months	9598	10764	1458	135.45 (128.67, 142.58)	1.33 (1.26, 1.40)
3 to 12 months	6969	11802	1546	130.99 (124.62, 137.68)	1.28 (1.22, 1.35)
More than 12 months	4171	12212	1586	129.86 (123.63, 136.41)	1.27 (1.21, 1.34)
Use status					
Current	9598	16576	1944	117.27 (112.17, 122.60)	1.15 (1.10, 1.20)
Recent	7685	1525	315	206.46 (184.87, 230.56)	2.02 (1.81, 2.26)
Past	6575	16677	2331	139.77 (134.21, 145.56)	1.37 (1.31, 1.43)
Time since discontinuation					
Concurrent	9598	16384	1905	116.27 (111.16, 121.61)	1.14 (1.09, 1.19)
Up to 3 months (1-89 days)	7858	2372	465	196.03 (179.00, 214.68)	1.92 (1.75, 2.10)
3 to 12 months	6262	4527	653	144.23 (133.58, 155.73)	1.41 (1.31, 1.53)
More than 12 months	4858	11495	1567	136.31 (129.73, 143.23)	1.33 (1.27, 1.41)

CI = confidence interval; MR = mortality rate; MRR = mortality rate ratio; N = number of patients; PY = person-years; US = United States.

Source: Appendix 3.1 Table 14

10.4.1.3 Adjusted Analyses of 5-Year All-cause Mortality for Ever-versus-never exposure to Roflumilast

Crude MRs, unadjusted and adjusted HRs of ever-versus-never exposure for 5-year all-cause mortality across study countries are summarised in Table 29. The crude and adjusted HRs

show that modelling of mortality as time to event with further adjustment for markers of COPD severity and morbidity beyond the PS matching at baseline reduced all the risk estimates towards 1. A statistically significant association between exposure to roflumilast and mortality risk for ever-versus-never exposure to roflumilast remained in GER and the US, while in SWE the adjusted HR was reduced to 0.98 (95% CI: 0.92, 1.04).

Table 29 Mortality Rates, Crude and Adjusted Hazard Ratios of 5-Year All-Cause Mortality for Ever-Versus-Never Exposure to Roflumilast

All-cause mortality	GER[a]	SWE	US
Number of ever exposed (PY)	8775 (34453)	3214 (12139)	9598 (34779)
Number of never exposed (PY)	41718 (160716)	15776 (57594)	47151 (171688)
Number of events (ever exposed)	3230	1475	4590
Number of events (never exposed)	12071	6104	17539
Mortality rate[b] ever exposed (95% CI)	93.75 (90.54, 97.04)	121.51 (115.46, 127.87)	131.97 (128.21, 135.85)
Mortality rate[b] never exposed (95% CI)	75.11 (73.77, 76.46)	105.98 (103.36, 108.68)	102.16 (100.66, 103.68)
Crude HR (95% CI)	1.17 (1.13, 1.22)	1.11 (1.05, 1.18)	1.25 (1.21, 1.29)
Adjusted[c] HR (95% CI)	1.12 (1.08, 1.17)	0.98 (0.92, 1.04)	1.16 (1.12, 1.20)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Mortality rate estimates per 1000 person-years at risk

[c] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity score; PY = person-year; SWE = Sweden; US = United States

Sources: Appendix 1 Table 10a, Table 35a1.1, Table 37a1.1a ; Appendix 2.1 Table 15; Appendix 3.1 Table 15

10.4.1.4 Adjusted Analyses of 5-Year All-cause Mortality for Current, Recent, and Past Use Versus Never Use of Roflumilast

Crude and adjusted HRs according to current, recent, and past roflumilast use versus never use are presented in Table 30 for GER, SWE, and the US. Adjustment for markers of COPD severity and morbidity beyond the PS matching at baseline consistently reduced all HRs across all exposure categories in all countries. After adjustment, there were statistically significantly elevated HRs during recent and past use in GER and the US and during past use in SWE compared to never use. For current use, no elevated risk was seen across the countries compared to never use, and a significant protective effect was observed in SWE. The numerically elevated HRs observed in association with recent use of roflumilast in GER and the US were further explored in the analyses in Table 49.

Table 30 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality for Current, Recent, and Past Use of Roflumilast Versus Never Use

All-cause mortality	GER[a]				SWE				US			
	Never (ref.)	Current	Recent	Past	Never (ref.)	Current	Recent	Past	Never (ref.)	Current	Recent	Past
Deaths (person-years)	12071 (160716)	1242 (15183)	201 (1481)	1787 (17790)	6104 (57594)	506 (5078)	62 (484)	907 (6575)	17539 (171688)	1944 (16576)	315 (1525)	2331 (16677)
N at risk	41718	8775	7255	6305	15776	3234	2520	2305	47151	9598	7685	6575
MR/1000 PY (95% CI)	75.11 (73.77, 76.46)	81.80 (77.32, 86.48)	135.73 (117.61, 155.84)	100.45 (95.85, 105.22)	105.98 (103.36, 108.68)	99.63 (91.31, 108.70)	127.93 (99.74, 164.08)	137.93 (129.24, 147.21)	102.16 (100.66, 103.68)	117.27 (112.17, 122.60)	206.46 (184.87, 230.56)	139.77 (134.21, 145.56)
Crude HR (95% CI)	1	0.94 (0.88, 0.99)	1.67 (1.45, 1.93)	1.36 (1.30, 1.43)	1	0.85 (0.77, 0.93)	1.06 (0.82, 1.36)	1.35 (1.26, 1.45)	1	1.06 (1.01, 1.11)	1.90 (1.70, 2.13)	1.40 (1.34, 1.46)
Adjusted[b] HR (95% CI)	1	0.93 (0.88, 0.98)	1.57 (1.37, 1.81)	1.26 (1.19, 1.32)	1	0.80 (0.73, 0.88)	0.93 (0.72, 1.20)	1.12 (1.04, 1.21)	1	1.00 (0.95, 1.04)	1.79 (1.60, 2.00)	1.28 (1.23, 1.34)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11a1.1, Table 35 a1.1, Table 37 a1.1b; Appendix 2.1 Table 16; Appendix 3.1 Table 16

10.4.1.5 Adjusted Analyses of 5-Year All-cause Mortality for Cumulative Roflumilast Exposure Duration Versus Never Use

Crude and adjusted HRs of all-cause mortality according to cumulative roflumilast exposure duration (Up to 3 months, 3 to 12 months, and >12 months) versus never use are presented in Table 31 for GER, SWE, and the US. With modelling of mortality as time-to-event, and further adjustment of HRs for variables related to COPD severity and morbidity, adjusted HRs were reduced across all exposure duration categories and all countries. In SWE, no elevation of risk for any of the cumulative exposure duration categories was observed in the adjusted analyses. There were significantly elevated HRs of mortality in GER for 3 to 12 months and >12 months and in the US for all exposure duration categories versus the unexposed.

Table 31 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality Associated with Cumulative Exposure to Roflumilast Versus Never Use

	GER[a]				SWE				US			
All-cause mortality	**Never (ref.)**	**Up to 3 months**	**3 to 12 months**	**>12 months**	**Never (ref.)**	**Up to 3 months**	**3 to 12 months**	**> 12 months**	**Never (ref.)**	**Up to 3 months**	**3 to 12 months**	**> 12 months**
Deaths (person-years)	12,071 (160716)	1053 (11916)	1129 (11457)	1048 (11081)	6104 (57594)	503 (3827)	586 (4686)	386 (3624)	17,539 (171688)	1458 (10764)	1546 (11802)	1586 (12212)
N at risk	41718	8775	6154	3642	15776	3234	2310	1171	47151	9598	6969	4171
MR/1000 PY (95% CI)	75.11 (73.77, 76.46)	88.37 (83.11, 93.87)	98.54 (92.88, 104.46)	94.58 (88.94, 100.48)	105.98 (103.36, 108.68)	131.42 (120.42, 143.42)	125.03 (115.31, 135.57)	106.49 (96.38, 117.66)	102.16 (100.66, 103.68)	135.45 (128.67, 142.58)	130.99 (124.62, 137.68)	129.86 (123.63, 136.41)
Crude HR (95% CI)	1	1.13 (1.06, 1.21)	1.26 (1.19, 1.34)	1.12 (1.05, 1.20)	1	1.17 (1.07, 1.28)	1.15 (1.06, 1.26)	0.99 (0.89, 1.10)	1	1.26 (1.19, 1.33)	1.26 (1.19, 1.32)	1.24 (1.17, 1.30)
Adjusted [b] HR (95% CI)	1	1.06 (0.99, 1.13)	1.18 (1.11, 1.26)	1.13 (1.06, 1.21)	1	0.99 (0.90, 1.08)	0.99 (0.91, 1.08)	0.94 (0.85, 1.05)	1	1.17 (1.10, 1.23)	1.17 (1.11, 1.24)	1.15 (1.09, 1.21)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years; ref. = reference; SWE = Sweden; US = United States.

Source: Appendix 1 Table 11a1.1, Table 35 a1.1, Table 37 a1.1c; Appendix 2.1 Table 17; Appendix 3.1 Table 17

Crude and adjusted HRs of 5-year all-cause mortality associated with cumulative exposure duration to roflumilast with the longest category of exposure split in two (ie, <3 months, 3 to 12 months, >12 to 24 months, and >24 months) versus never exposure are presented for GER, SWE, and the US in Table 32.

After adjustment, no consistent pattern of elevated risk for a particular duration category was apparent across the countries. In SWE, no elevation of risk was observed for any duration category. In GER, a statistically significant increase in 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.

Table 32 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality Associated with Cumulative Use (<3 months, 3 to 12 months, >12 to 24 months, >24 months) of Roflumilast Versus Never Use

Country	All-cause mortality	Never (ref.)	<3 months	3 to 12 months	>12 to 24 months	>24 months
GER[a]	Deaths (person-years)	12071 (160716)	1053 (11916)	1129 (11457)	489 (4823)	559 (6258)
	N at risk	41718	8775	6154	3642	2754
	Crude HR (95% CI)	1	1.13 (1.06, 1.21)	1.26 (1.19, 1.34)	1.26 (1.15, 1.38)	1.02 (0.94, 1.12)
	Adjusted[b] HR (95% CI)	1	1.06 (0.99, 1.13)	1.18 (1.11, 1.26)	1.24 (1.13, 1.35)	1.05 (0.96, 1.15)
SWE	Deaths (person-years)	6104 (57594)	503 (3827)	586 (4686)	169 (1544)	217 (2079)
	N at risk	15776	3234	2310	1171	880
	Crude HR (95% CI)	1	1.17 (1.07, 1.28)	1.15 (1.06, 1.26)	1.00 (0.86, 1.17)	0.98 (0.85, 1.12)
	Adjusted[b] HR (95% CI)	1	0.99 (0.90, 1.08)	0.99 (0.91, 1.08)	0.96 (0.82, 1.12)	0.94 (0.81, 1.08)
US	Deaths (person-years)	17539 (171688)	1458 (10764)	1546 (11802)	683 (5427)	903 (6785)
	N at risk	47151	9598	6969	4171	3062
	Crude HR (95% CI)	1	1.26 (1.19, 1.33)	1.26 (1.19, 1.32)	1.21 (1.12, 1.31)	1.26 (1.17, 1.34)
	Adjusted[b] HR (95% CI)	1	1.17 (1.10, 1.23)	1.17 (1.11, 1.24)	1.12 (1.04, 1.21)	1.17 (1.10, 1.26)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; PS = propensity score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11a1.1, Table 11i, Table 35a1.2, Table 37 a1.1c, Table 37 a1.2; Appendix 2.1 Table 20, Appendix 3.1 Table 20

10.4.1.6 Adjusted Analyses of 5-Year All-cause Mortality by Time Since Roflumilast Discontinuation Versus Never Exposure to Roflumilast

Table 33 presents unadjusted and adjusted HRs of 5-year all-cause mortality associated with time since roflumilast exposure discontinuation versus never use in all countries. As in all previous analyses, the adjustment for variables related to COPD severity and morbidity reduced the HRs across all categories and all countries.

No elevation of risk of mortality was observed in GER, SWE, and the US for concurrent versus never use of roflumilast based on the adjusted HR. The HRs in GER and SWE for the concurrent use showed a significant protective effect. A statistically significant increase in risk that was observed after discontinuation of roflumilast declined with the duration of discontinuation in GER and the US while no significantly elevated risk of mortality was observed in SWE after discontinuation of roflumilast up to 12 months.

Table 33 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality Associated With Time Since Discontinuation of Roflumilast Versus Never Use

All-cause mortality	GER[a]				SWE				US			
	Con-current	Up to 3 months	3 to 12 months	>12 months	Con-current	Up to 3 months	3 to 12 months	>12 months	Con-current	Up to 3 months	3 to 12 months	>12 months
Deaths (PY)	1219 (15010)	288 (2265)	470 (4544)	1253 (12634)	496 (5025)	106 (764)	216 (1670)	657 (4677)	1905 (16384)	465 (2372)	653 (4527)	1567 (11495)
N at risk	8775	7397	6044	4909	3234	2582	2232	1869	9598	7858	6262	4858
MR/1000 PY (95% CI)	81.22 (76.72, 85.91)	127.14 (112.88, 142.71)	103.42 (94.28, 113.21)	99.18 (93.76, 104.82)	98.70 (90.38, 107.78)	138.60 (114.57, 167.66)	129.27 (113.13, 147.71)	140.45 (130.11, 151.61)	116.27 (111.16, 121.61)	196.03 (179.00, 214.68)	144.23 (133.58, 155.73)	136.31 (129.73, 143.23)
Crude HR (95% CI)	0.93 (0.88, 0.99)	1.59 (1.41, 1.79)	1.42 (1.29, 1.55)	1.34 (1.27, 1.43)	0.84 (0.77, 0.92)	1.17 (0.96, 1.42)	1.22 (1.06, 1.40)	1.40 (1.28, 1.51)	1.05 (1.00, 1.10)	1.81 (1.65, 1.99)	1.40 (1.29, 1.51)	1.39 (1.32, 1.46)
Adjusted[b] HR (95% CI)	0.93 (0.87, 0.98)	1.49 (1.32, 1.68)	1.30 (1.19, 1.43)	1.24 (1.17, 1.32)	0.79 (0.72, 0.87)	1.02 (0.84, 1.24)	1.04 (0.90, 1.20)	1.15 (1.05, 1.25)	0.99 (0.94, 1.04)	1.70 (1.55, 1.86)	1.28 (1.19, 1.39)	1.27 (1.20, 1.34)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex +country specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11a1.1, Table 35a1.1, Table 37 a1.1d; Appendix 2.1 Table 18; Appendix 3.1 Table 18

10.4.1.7 Adjusted Analyses of 5-Year All-cause Mortality for Ever-versus-never exposure to Roflumilast by PS Quintiles

Table 34 presents adjusted HRs of 5-year all-cause mortality for ever-versus-never exposure to roflumilast in subpopulations defined by the 5 PS quintiles as a proxy for COPD severity (with the first quintile indicating lowest and the fifth quintile indicating highest COPD severity).

There was a strong trend showing the highest HR of increased risk in the first quintile (lower PS) for GER and for the US, and the lowest risk in the fifth quintile (highest PS) in all countries. The HRs in GER and SWE for the fifth quintile showed a significant protective effect.

Table 34 Adjusted Hazard Ratios of 5-Year All-cause Mortality for Ever-Versus-Never Use of Roflumilast Stratified by PS Quintile

Propensity score quintiles	Adjusted[a] Hazard Ratio (95% CI)		
	GER	SWE	US
First quintile	1.56 (1.40; 1.73)	1.12 (0.96, 1.30)	1.29 (1.18, 1.41)
Second quintile	1.26 (1.15; 1.39)	1.13 (0.98, 1.31)	1.25 (1.15, 1.36)
Third quintile	1.09 (1.00; 1.20)	0.95 (0.83, 1.09)	1.23 (1.14, 1.33)
Fourth quintile	1.12 (1.03; 1.22)	0.91 (0.80, 1.04)	1.14 (1.06, 1.22)
Fifth quintile	0.90 (0.83, 0.97)	0.87 (0.77, 0.99)	1.01 (0.94, 1.08)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching in any of the 5 PS quintiles (Table 14) + markers of COPD severity and morbidity (Table 10).

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity score; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 37 a4.1, Table 37 a4.2, Table 37 a4.3, Table 37 a4.4, Table 37 a4.5; Appendix 2.1 Table 21; Appendix 3.1 Table 21

10.4.2 Adjusted Secondary and Exploratory Outcomes

Except for malignant neoplasms, which are expected to have a long latency, the main exposure category for secondary outcomes was considered to be current exposure of roflumilast (against the reference never use). Time to event was analysed using a Cox proportional hazard model adjusting for age, sex, country-specific imbalanced variables after PS matching and variables related to healthcare utilisation and outcome-specific risk factors.

Crude and adjusted HRs for secondary outcomes for current, recent, and past use versus never use of roflumilast in GER, SWE, and the US are presented in Table 35.

Whereas adjustment for relevant covariables consistently reduced the risk estimates for respiratory disease-related hospitalisations and all-cause hospitalisations, the effect of adjustment on the other outcomes was less consistent and often had smaller effects. Adjusted HRs for respiratory disease-related hospitalisation and hospitalisation for any cause showed a statistically significant risk increase in all countries for current use, with a similar magnitude of risk increase also for recent and past use.

An increase in the risk of new diagnosis of depression was observed in GER, SWE, and the US. Point estimates of the HR were similar in GER and SWE. The risk of abnormal and unexplained weight loss showed elevated HRs that were significant for current use of roflumilast in GER and the US while in SWE, a significant increase of risk was observed during recent use of roflumilast. The risk of hospitalisation due to diarrhoea of non-infectious origin was significantly elevated in the US and SWE but not in GER for current use; all 3 countries showed elevated point estimates for recent use. No increased risk was seen for hospitalisation due to pulmonary embolism associated with current roflumilast use in any country, but a statistically significant increase was observed for past use of roflumilast in GER and SWE. Similarly, although no significant risk increases were seen for current use, a statistically significant association between new diagnoses of tuberculosis or hepatitis B or C or other severe viral hepatitis (except hepatitis A) and recent use of roflumilast was observed in GER and the US, based on small numbers.

Table 35 Crude and Adjusted Hazard Ratios for Secondary Outcomes for Current, Recent, and Past Use Versus Never Use of Roflumilast

	Crude HRs (95% CI)			Adjusted [a] HRs (95% CI)		
	Current use	**Recent use**	**Past use**	**Current use**	**Recent use**	**Past use**
Respiratory disease-related hospitalisation						
GER	1.59 (1.53, 1.66)	1.67 (1.50, 1.87)	1.64 (1.57, 1.72)	1.57 (1.51, 1.63)	1.64 (1.47, 1.83)	1.59 (1.53, 1.67)
SWE	1.50 (1.42, 1.60)	1.87 (1.58, 2.21)	1.60 (1.49, 1.72)	1.32 (1.24, 1.41)	1.64 (1.39, 1.94)	1.43 (1.33, 1.54)
US	1.41 (1.35, 1.47)	1.61 (1.44, 1.80)	1.47 (1.40, 1.54)	1.33 (1.28, 1.39)	1.53 (1.37, 1.70)	1.41 (1.34, 1.48)
Hospitalisation for any cause						
GER	1.23 (1.19, 1.26)	1.21 (1.11, 1.31)	1.20 (1.15, 1.24)	1.21 (1.18, 1.25)	1.21 (1.11, 1.31)	1.19 (1.14, 1.23)
SWE	1.21 (1.15, 1.28)	1.31 (1.13, 1.52)	1.25 (1.17, 1.34)	1.13 (1.08, 1.20)	1.22 (1.05, 1.42)	1.15 (1.08, 1.23)
US	1.16 (1.12, 1.20)	1.20 (1.10, 1.31)	1.16 (1.11, 1.20)	1.12 (1.09, 1.16)	1.18 (1.09, 1.29)	1.13 (1.09, 1.17)
New diagnosis of depression						
GER	1.58 (1.29, 1.93)	2.05 (1.19, 3.52)	1.41 (1.15, 1.74)	1.58 (1.29, 1.93)	2.01 (1.17, 3.45)	1.36 (1.11, 1.68)
SWE	1.52 (0.59, 3.94)	-	1.37 (0.53, 3.54)	1.69 (0.64, 4.46)	-	1.66 (0.63, 4.39)
US	1.37 (1.26, 1.48)	1.71 (1.37, 2.13)	1.17 (1.07, 1.28)	1.36 (1.25, 1.48)	1.67 (1.33, 2.09)	1.13 (1.04, 1.24)
Hospitalisation for suicide attempt						
GER	1.14 (0.78, 1.67)	1.35 (0.49, 3.69)	1.51 (1.09, 2.09)	1.15 (0.79, 1.70)	1.37 (0.50, 3.74)	1.50 (1.08, 2.08)
SWE	0.80 (0.37, 1.73)	-	1.17 (0.64, 2.14)	0.70 (0.32, 1.55)	-	1.08 (0.58, 2.03)

Table 35 Crude and Adjusted Hazard Ratios for Secondary Outcomes for Current, Recent, and Past Use Versus Never Use of Roflumilast

	Crude HRs (95% CI)			Adjusted [a] HRs (95% CI)		
	Current use	**Recent use**	**Past use**	**Current use**	**Recent use**	**Past use**
US	1.08 (0.81, 1.44)	1.22 (0.45, 3.27)	0.90 (0.69, 1.19)	1.04 (0.78, 1.38)	1.12 (0.41, 3.01)	0.88 (0.67, 1.16)
Hospitalisation due to diarrhoea of non-infectious origin						
GER	1.05 (0.70, 1.56)	1.76 (0.65, 4.81)	1.00 (0.69, 1.45)	1.07 (0.71, 1.59)	1.66 (0.61, 4.53)	0.94 (0.65, 1.37)
SWE	1.57 (1.11, 2.22)	1.69 (0.62, 4.60)	1.15 (0.79, 1.67)	1.55 (1.08, 2.24)	1.55 (0.57, 4.25)	1.05 (0.71, 1.54)
US	1.25 (1.09, 1.43)	1.34 (0.91, 1.96)	1.07 (0.91, 1.24)	1.24 (1.08, 1.42)	1.30 (0.89, 1.92)	1.05 (0.90, 1.23)
Abnormal and unexplained weight loss						
GER	2.45 (1.63, 3.69)	NA	0.96 (0.56, 1.64)	2.49 (1.65, 3.76)	NA	0.91 (0.53, 1.57)
SWE	1.56 (0.89, 2.73)	3.52 (1.08, 11.50)	1.38 (0.82, 2.31)	1.57 (0.88, 2.83)	3.38 (1.03, 11.13)	1.38 (0.81, 2.35)
US	1.73 (1.63, 1.83)	1.21 (0.99, 1.47)	1.04 (0.96, 1.11)	1.76 (1.67, 1.86)	1.21 (0.99, 1.48)	1.03 (0.95, 1.10)
Hospitalisations due to major cardiovascular events						
GER	0.94 (0.87, 1.02)	1.13 (0.90, 1.41)	1.11 (1.04, 1.19)	0.96 (0.89, 1.04)	1.14 (0.91, 1.43)	1.13 (1.06, 1.22)
SWE	0.84 (0.73, 0.96)	1.32 (0.94, 1.86)	1.15 (1.03, 1.29)	0.84 (0.73, 0.96)	1.25 (0.89, 1.76)	1.09 (0.97, 1.22)
US	0.94 (0.87, 1.03)	1.27 (1.01, 1.58)	0.99 (0.91, 1.08)	0.93 (0.86, 1.02)	1.28 (1.02, 1.60)	1.00 (0.92, 1.09)
Hospitalisations due to arrhythmia						
GER	0.55 (0.33, 0.92)	0.84 (0.21, 3.43)	1.02 (0.73, 1.43)	0.60 (0.36, 1.00)	0.86 (0.21, 3.52)	1.03 (0.73, 1.44)
SWE	0.99 (0.53, 1.84)	1.89 (0.46, 7.85)	0.89 (0.51, 1.55)	1.07 (0.56, 2.02)	1.77 (0.42, 7.43)	0.82 (0.46, 1.45)
US	0.97 (0.45, 2.09)	NA	0.51 (0.22, 1.16)	0.92 (0.43, 1.99)	NA	0.51 (0.22, 1.16)
Hospitalisations due to myocardial infarction						
GER	0.92 (0.78, 1.08)	1.20 (0.76, 1.90)	1.12 (0.97, 1.28)	0.93 (0.79, 1.09)	1.18 (0.74, 1.86)	1.10 (0.96, 1.26)
SWE	0.81 (0.62, 1.05)	1.20 (0.60, 2.43)	1.20 (0.98, 1.47)	0.79 (0.60, 1.03)	1.14 (0.56, 2.31)	1.13 (0.92, 1.40)
US	1.04 (0.88, 1.23)	1.32 (0.84, 2.09)	1.07 (0.91, 1.25)	1.02 (0.87, 1.21)	1.32 (0.84, 2.08)	1.08 (0.92, 1.26)

Table 35 Crude and Adjusted Hazard Ratios for Secondary Outcomes for Current, Recent, and Past Use Versus Never Use of Roflumilast

	Crude HRs (95% CI)			Adjusted [a] HRs (95% CI)		
	Current use	Recent use	Past use	Current use	Recent use	Past use
Hospitalisations due to cerebral infarction						
GER	0.78 (0.64, 0.95)	1.09 (0.61, 1.93)	1.03 (0.88, 1.20)	0.83 (0.68, 1.02)	1.11 (0.62, 1.97)	1.04 (0.88, 1.21)
SWE	0.69 (0.49, 0.99)	1.50 (0.70, 3.20)	0.89 (0.68, 1.18)	0.75 (0.52, 1.08)	1.51 (0.70, 3.23)	0.88 (0.66, 1.17)
US	0.93 (0.78, 1.12)	1.19 (0.73, 1.96)	0.95 (0.80, 1.14)	0.94 (0.78, 1.12)	1.21 (0.74, 1.99)	0.97 (0.81, 1.16)
Hospitalisations due to heart failure						
GER	1.05 (0.95, 1.16)	1.17 (0.87, 1.58)	1.04 (0.94, 1.14)	1.07 (0.97, 1.19)	1.23 (0.92, 1.65)	1.10 (1.00, 1.21)
SWE	0.91 (0.75, 1.10)	1.09 (0.64, 1.85)	1.12 (0.95, 1.31)	0.88 (0.73, 1.07)	0.98 (0.58, 1.68)	0.99 (0.84, 1.17)
US	0.95 (0.84, 1.07)	1.38 (1.02, 1.85)	1.00 (0.88, 1.13)	0.91 (0.81, 1.03)	1.39 (1.03, 1.87)	1.02 (0.90, 1.16)
Hospitalisations due to pulmonary embolism						
GER	0.72 (0.54, 0.95)	1.11 (0.52, 2.35)	1.42 (1.16, 1.73)	0.72 (0.55, 0.96)	1.09 (0.51, 2.31)	1.37 (1.12, 1.67)
SWE	0.74 (0.51, 1.08)	1.40 (0.57, 3.43)	1.56 (1.22, 2.01)	0.74 (0.50, 1.10)	1.34 (0.55, 3.29)	1.49 (1.15, 1.93)
US	0.74 (0.54, 1.01)	1.18 (0.52, 2.65)	1.23 (0.95, 1.58)	0.74 (0.54, 1.01)	1.18 (0.52, 2.65)	1.23 (0.95, 1.58)
New diagnoses of tuberculosis or hepatitis B or C or other severe viral hepatitis (except hepatitis A)						
GER	1.06 (0.37, 3.01)	6.55 (1.45, 29.47)	NA	0.92 (0.32, 2.63)	5.80 (1.29, 26.03)	NA
SWE	1.43 (0.55, 3.70)	-	0.56 (0.13, 2.35)	1.49 (0.55, 3.99)	-	0.61 (0.14, 2.62)
US	0.97 (0.74, 1.27)	1.90 (1.01, 3.59)	1.09 (0.85, 1.41)	0.97 (0.74, 1.27)	1.90 (1.01, 3.58)	1.09 (0.85, 1.41)

[a] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 14) + outcome-specific variables (Appendix 8). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; GER = Germany; HR = hazard ratio; NA = not available; PS = propensity score; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 39 a390, Table 40, Table 41, Table 42, Table 43, Table 44, Table 45, Table 46, Table 47a, Table 50, Table 51, Table 52, Table 53 a2.1a, Table 54 b1, Table 55 a1, Table 56 b1, Table 57 b1, Table 58 b1, Table 59 b1, Table 60 a1, Table 61 b1, Table 62 b1, Table 64 b1, Table 65 b1, Table 66 b1; Appendix 2.1 Table 22 (SWE); Appendix 3.1 Table 22

Hospitalisation for suicide attempt showed no significant or consistent risk increase across countries for current use (Table 35). This outcome was explored in more detail. Table 36

presents detailed results on the association of roflumilast exposure with hospitalisation for suicide attempt in GER, SWE, and the US excluding and including patients with prior suicide attempt. Overall, the number of suicide attempts was very small in all countries, and excluding patients with prior suicide attempt reduced the number of events only by a very small number. Due to the small number of events, CIs were very wide and none of the risk estimates were statistically significant, except for past use in GER, and point estimates for current use were close to or even below 1. For patients with recent use of roflumilast, only 4 events in GER, 4 events in the US, and no events in SWE were identified.

Table 36 Crude IRs, Crude and Adjusted Hazard Ratios of Hospitalisation for Suicide Attempt Per 10,000 Person-Years for Current, Recent, and Past Roflumilast Exposure Compared to Never Exposure Excluding and Including Patients With Prior Suicide Attempt

Exposure	N events	PY	Crude IR (95% CI)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
GER					
Excluding patients with prior suicide attempt					
Current use	30	18022	16.65 (11.23, 23.76)	1.14 (0.78, 1.67)	1.15 (0.79, 1.70)
Recent use	4	1596	25.06 (6.83, 64.17)	1.35 (0.49, 3.69)	1.37 (0.50, 3.74)
Past use	43	23516	18.29 (13.23, 24.63)	1.51 (1.09, 2.09)	1.50 (1.08, 2.08)
Never use	255	202522	12.59 (11.09, 14.24)	1.00	1.00
Including patients with prior suicide attempt					
Current use	31	18053	17.17 (11.67, 24.37)	1.13 (0.78, 1.65)	1.16 (0.80, 1.69)
Recent use	4	1599	25.01 (6.82, 64.05)	1.30 (0.48, 3.54)	1.34 (0.49, 3.66)
Past use	43	23554	18.26 (13.21, 24.59)	1.47 (1.06, 2.04)	1.48 (1.07, 2.06)
Never use	263	203183	12.94 (11.43, 14.61)	1.00	1.00
SWE					
Excluding patients with prior suicide attempt					
Current use	7	5737	12.20 (5.82, 25.59)	0.80 (0.37, 1.73)	0.70 (0.32, 1.55)
Recent use	0	502	-	-	-
Past use	12	8146	14.73 (8.37, 25.94)	1.17 (0.64, 2.14)	1.08 (0.58, 2.03)
Never use	92	67387	13.65 (11.13, 16.75)	1	1
Including patients with prior suicide attempt					
Current use	10	5860	17.07 (9.18, 31.72)	0.92 (0.48, 1.76)	0.80 (0.41, 1.57)
Recent use	0	511	-	-	-
Past use	13	8267	15.73 (9.13, 27.08)	1.02 (0.58, 1.82)	0.94 (0.52, 1.71)
Never use	115	69775	16.48 (13.73, 19.79)	1	1
US					
Excluding patients with prior suicide attempt					
Current use	52	18429	28.22 (21.50, 37.03)	1.08 (0.81, 1.44)	1.04 (0.78, 1.38)
Recent use	4	1593	25.10 (9.42, 66.87)	1.22 (0.45, 3.27)	1.12 (0.41, 3.01)
Past use	56	20190	27.74 (21.35, 36.04)	0.90 (0.69, 1.19)	0.88 (0.67, 1.16)
Never use	564	199304	28.30 (26.06, 30.73)	1	1
Including patients with prior suicide attempt					
Current use	53	18499	28.65 (21.89, 37.50)	1.04 (0.78, 1.38)	1.01 (0.76, 1.34)
Recent use	4	1604	24.94 (9.36, 66.46)	1.10 (0.41, 2.97)	1.02 (0.38, 2.75)
Past use	58	20299	28.57 (22.09, 36.96)	0.90 (0.69, 1.18)	0.88 (0.67, 1.16)
Never use	593	200987	29.50 (27.22, 31.98)	1	1

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + outcome-specific variables (Appendix 8). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; GER = Germany; HR = hazard ratio; IR = incidence rate; NA = not available; PS = propensity score; PY = person-years; SWE = Sweden; US = United States

Sources: Appendix 1 Table 13 a1, Table 13 a2, Table 39 a391, Table 53 a2.1a, Table 53 a2.1b; Appendix 2.1 Table 23; Appendix 3.1 Table 23

Crude and adjusted HRs for new diagnosis of malignant neoplasm based on ever-versus-never use of roflumilast applying latency periods of 1 and 2 years are presented in Table 37. In GER and the US, adjusted HRs showed slightly elevated risk estimates with statistical significance for ever use of roflumilast irrespective of the latency assumption used (none, 1 year, or 2 years. In GER and the US, adjusted HRs showed slightly elevated risk estimates with statistical significance for ever use of roflumilast irrespective of the latency assumption used (no latency, 1-year or 2-years latency). In SWE, the increase in risk was not significantly elevated for no latency and 2-years latency and borderline significant for 1-year latency assumption.

Table 37 Crude and Adjusted Hazard Ratios of New Diagnosis of Malignant Neoplasm for Ever-Versus-Never Use of Roflumilast Per Country, Applying No Latency Period and Latency Periods of 1 and 2 Years

Outcomes	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
New diagnosis of malignant neoplasm		
GER	1.07 (1.01, 1.13)	1.09 (1.03, 1.15)
SWE	1.17 (1.05, 1.31)	1.12 (1.00, 1.27)
US	1.10 (1.03, 1.17)	1.09 (1.02, 1.17)
New diagnosis of malignant neoplasm with 1 year latency		
GER	1.23 (1.14, 1.33)	1.22 (1.13, 1.31)
SWE	1.20 (1.05, 1.36)	1.15 (1.00, 1.32)
US	1.14 (1.05, 1.23)	1.12 (1.04, 1.21)
New diagnosis of malignant neoplasm with 2 years latency		
GER	1.22 (1.12, 1.33)	1.20 (1.10, 1.31)
SWE	1.17 (1.00, 1.35)	1.12 (0.95, 1.31)
US	1.16 (1.06, 1.27)	1.14 (1.04, 1.25)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + outcome-specific variables (Appendix 8). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity score; SWE = Sweden; US = United States

Sources: Appendix 1 Table 49a1, Table 49a2, Table 49a3, Table 63 a1.1, Table 63 a2.1, Table 63 a3.1; Appendix 2.1 Table 24; Appendix 3.1 Table 24

Analyses stratifying malignant neoplasms into solid and haematopoietic tumours were performed in all countries (Table 38). Results for solid tumours were similar to those for any

malignancy, as expected given that the vast majority of malignancies are solid tumours. No clear differences were observed for diverse latency allowance.

For hematopoietic tumours, no significant estimates were seen. In SWE and the US, the lowest point estimates (below 1) for hematopoietic tumours were seen for long latency.

Table 38 Crude and Adjusted Hazard Ratios for Solid and Haematopoietic Tumours for Ever-Versus-Never Use of Roflumilast

Latency	GER		SWE		US	
	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Solid tumours						
No latency	1.09 (1.03, 1.15)	1.11 (1.05, 1.17)	1.08 (0.98, 1.18)	1.03 (0.94, 1.14)	1.04 (0.98, 1.11)	1.04 (0.98, 1.11)
1-year latency	1.24 (1.15, 1.34)	1.23 (1.14, 1.33)	1.23 (1.08, 1.40)	1.17 (1.02, 1.35)	1.17 (1.08, 1.26)	1.15 (1.06, 1.25)
2-year latency	1.23 (1.13, 1.35)	1.21 (1.11, 1.33)	1.20 (1.04, 1.40)	1.15 (0.98, 1.35)	1.20 (1.09, 1.32)	1.18 (1.07, 1.30)
Haematopoietic tumours						
No latency	0.78 (0.63, 0.96)	0.80 (0.65, 0.99)	0.78 (0.56, 1.08)	0.76 (0.54, 1.07)	0.79 (0.66, 0.95)	0.79 (0.66, 0.94)
1-year latency	1.05 (0.79, 1.40)	1.06 (0.80, 1.42)	0.68 (0.37, 1.26)	0.67 (0.35, 1.29)	0.76 (0.57, 1.00)	0.73 (0.55, 0.97)
2-year latency	0.91 (0.65, 1.27)	0.91 (0.65, 1.28)	0.51 (0.23, 1.13)	0.46 (0.20, 1.05)	0.68 (0.48, 0.96)	0.65 (0.46, 0.91)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + outcome-specific variables (Appendix 8). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country. Analysis stratified by different latency exposures for solid and haematopoietic tumours

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity score; SWE = Sweden; US = United States

Sources: Appendix 1 Table 49b1, Table 49b2, Table 49b3, Table 49c1, Table 49c2, Table 49c3, Table 63 b1.1, Table 63 b2.1, Table 63 b3.1, Table 63 c1.1, Table 63 c2.1, Table 63 c3.1; Appendix 2.1 Table 25; Appendix 3.1 Table 25

In SWE, where cancer registry data are available, the distributions of type of solid or haematopoietic tumours were analysed (Table 39 and Table 40, respectively). Among solid tumours, neoplasms of bronchus and lung were the most frequent and contributed 31.9% of all tumours in the exposed and 27.5% in the unexposed group (p=0.158) followed by neoplasms of the digestive organs (28.6% and 22.7%, respectively; p=0.044). However, the global p-value of 0.144 did not reveal any statistically significant difference in the total overall distribution of solid tumour types between the 2 groups. For haematopoietic tumours, the number of each tumour type was very small in the exposed (N=12) and unexposed groups (N=66). No conspicuous accumulation of a particular type of haematopoietic tumour was observed in association with roflumilast exposure (global p=0.171).

Table 39 Number and Percentage of Solid Tumours by Tumour Type and Exposure Status in SWE

Tumour type	Diagnosis code	Unexposed N (%)	Exposed N (%)	Total N (%)	P-value[a]
Malignant neoplasms of lip, oral cavity and pharynx	C00-C14	22 (2.39)	6 (1.97)	28 (2.29)	0.843
Malignant neoplasms of digestive organs	C15-C26	209 (22.69)	87 (28.62)	296 (24.16)	0.044
Malignant neoplasms of respiratory and intrathoracic organs	C30-C33, C37-C39	11 (1.19)	2 (0.66)	13 (1.06)	0.639
Malignant neoplasm of bronchus and lung	C34	253 (27.47)	97 (31.91)	350 (28.57)	0.158
Malignant neoplasms of bone and articular cartilage	C40-C41	1 (0.11)	0 (0.00)	1 (0.08)	1.000
Melanoma and other malignant neoplasms of skin	C43	45 (4.89)	7 (2.30)	52 (4.24)	0.076
Malignant neoplasms of mesothelial and soft tissue	C45-C49	6 (0.65)	1 (0.33)	7 (0.57)	0.835
Malignant neoplasms of breast	C50	83 (9.01)	24 (7.89)	107 (8.73)	0.630
Malignant neoplasms of female genital organs	C51-C58	38 (4.13)	7 (2.30)	45 (3.67)	0.197
Malignant neoplasms of male genital organs	C60-C63	109 (11.83)	23 (7.57)	132 (10.78)	0.048
Malignant neoplasms of urinary tract	C64-C68	86 (9.34)	32 (10.53)	118 (9.63)	0.619
Malignant neoplasms of eye, brain and other parts of central nervous system	C69-C72	12 (1.30)	2 (0.66)	14 (1.14)	0.544
Malignant neoplasms of thyroid and other endocrine glands	C73-C75	3 (0.33)	2 (0.66)	5 (0.41)	0.788
Malignant neoplasms of ill-defined, other secondary and unspecified sites	C76-C80	43 (4.67)	14 (4.61)	57 (4.65)	1.000
Total	-	921 (100)	304 (100)	1225 (100)	-

[a] Test for equal proportions (Pearson's chi-squared test)

Percentages are based on total numbers of events.

Global p-value (Fisher's exact test) for equal cancer distribution among exposed and unexposed: p=0.144

N = number of patients; SWE = Sweden.

Source: Appendix 2.1 Table 26

Table 40 Number and Percentage of Haematopoietic Tumours by Tumour Type and Exposure Status in SWE

Tumour type	Diagnosis code	Unexposed N (%)	Exposed N (%)	Total N (%)	P-value[a]
Hodgkin lymphoma	C81	1 (1.52)	0 (0.00)	1 (1.28)	1.000
Follicular lymphoma	C82	3 (4.55)	1 (8.33)	4 (5.13)	1.000
Non-follicular lymphoma	C83	14 (21.21)	0 (0.00)	14 (17.95)	0.176
Mature T/NK-cell lymphomas	C84	0 (0.00)	1 (8.33)	1 (1.28)	0.334
Other specified and unspecified types of non-Hodgkin lymphoma	C85	5 (7.58)	2 (16.67)	7 (8.97)	0.642
Malignant immunoproliferative diseases and certain other B-cell lymphomas	C88	3 (4.55)	1 (8.33)	4 (5.13)	1.000
Multiple myeloma and malignant plasma cell neoplasms	C90	12 (18.18)	2 (16.67)	14 (17.95)	1.00
Lymphoid leukaemia	C91	10 (15.15)	3 (25.00)	13 (16.67)	0.674
Myeloid leukaemia	C92	13 (19.70)	1 (8.33)	14 (17.95)	0.593
Monocytic leukaemia	C93	2 (3.03)	0 (0.00)	2 (2.56)	1.000
Other leukaemia's of specified cell type	C94	1 (1.52)	1 (8.33)	2 (2.56)	0.703
Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue	C96	2 (3.03)	0 (0.00)	2 (2.56)	1.000
Total	-	66 (100)	12 (100)	78 (100)	-

[a] Test for equal proportions (Pearson's chi-square test)

Percentages are based on total numbers of events.

Global p-value (Fisher's exact test) for equal cancer distribution among exposed and unexposed: p=0.171.

N = number of patients; NK = natural killer; SWE = Sweden

Source: Appendix 2.1 Table 27

In the exploratory analyses of cause-specific mortality in SWE, no increase in risk was seen for cardiovascular-disease related deaths and respiratory-disease related deaths. An elevated risk was seen for cancer-related deaths, with the adjusted HRs for ever use of roflumilast versus never use of 1.34 (95% CI: 1.26, 1.44) while increased risk of death for other causes was not significant (Table 41).

Table 41 Crude and Adjusted Hazard Ratios for Exploratory Cause-Specific Mortality Outcomes for Ever-Versus-Never Use of Roflumilast in SWE

Exploratory outcomes	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Cancer related deaths	0.80 (0.63, 1.00)	1.34 (1.26, 1.44)
Cardiovascular disease related deaths	0.78 (0.66, 0.92)	0.87 (0.75, 1.01)
Respiratory disease related deaths	1.06 (0.98, 1.15)	0.88 (0.73, 1.07)
Other causes	0.98 (0.86, 1.11)	1.05 (0.94, 1.17)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PS = propensity scores; SWE = Sweden

Source: Appendix 2.1 Table 28

10.5 Additional Analyses - Sensitivity Analyses

10.5.1 Sensitivity Analyses for the Primary Outcome

Several sensitivity analyses were conducted in all study countries to test the robustness of the results of the main analyses of 5-year all-cause mortality according to ever-versus-never use of roflumilast.

10.5.1.1 Sensitivity Analysis Excluding Bias Due to Use as Last Resort

Roflumilast might have been used as a last resort in patients severely ill and who were likely to die soon. Sensitivity analyses were therefore performed for 5-year all-cause mortality by excluding deaths in the first 3 and 12 months after CED in GER, SWE, and the US (Table 50, Table 51, and Table 52). Ever-exposed patients with a mortality event within the 3 or 12 months after CED were excluded together with their controls in this analysis. In GER, the sensitivity analysis resulted in lower point estimates for the adjusted HR compared to the main analysis. In SWE and the US, the sensitivity analyses resulted in slightly higher point estimates for crude and adjusted HRs than the main ever-versus-never analysis for SWE and the US.

10.5.1.2 Sensitivity Analysis With Respect to Time Period of Gap Extension

Sensitivity analyses for 5-year all-cause mortality were performed to determine whether the gap extension period applied in constructing exposure status affected the mortality risk observed for current, recent, and past roflumilast users versus never users (Table 53).

In GER and SWE no gap extension and 100% gap extension showed comparable point estimates and similar pattern to that observed in the main analysis of current, recent, and past use versus never use described in Table 30. In the US, a gap extension of 100% raised the adjusted HR only for current use of roflumilast while the adjusted HR was reduced during recent use. Without gap extension in the US, this increase was observed only for recent use while the adjusted HR was reduced during current use.

10.5.1.3 Sensitivity Analysis with Respect to Early Discontinuation: Analysis by Number of Roflumilast Dispensations

All-cause mortality according to ever-versus-never use of roflumilast was further investigated with follow-up time stratified by the number of roflumilast dispensations throughout follow-up.

The number of roflumilast dispensations were categorised as 1, 2 to 3, 4 to 9 and ≥10 (Table 54). In GER, there was a significantly elevated risk of mortality for each category of number of dispensations versus never use. There was a significantly elevated risk of mortality for 1 dispensation in all countries, 2 to 3 dispensations in GER and the US only, and 4 to

9 dispensations in all countries, ≥10 dispensations in GER only. In SWE and the US, the mortality risk was reduced for ≥10 dispensations of roflumilast compared to never use.

10.5.1.4 Sensitivity Analysis by FEV_1

Since FEV_1 can be considered a marker of COPD severity, a stratified analysis of 5-year all-cause mortality of ever versus never roflumilast use was performed and is summarised in Table 55. The GER database is the only database which contains information on FEV_1, and FEV_1 records are mostly available for patients hospitalised, ie, presumably patients with more severe COPD. In this analysis, FEV_1 records were available for approximately 79% of roflumilast exposed and matched unexposed patients.

In patients in whom the FEV_1 value was not specified, the adjusted HR was statistically significant at 1.36 (95% CI: 1.24, 1.49). Crude and adjusted HRs were comparable in patients with FEV_1 values between 50% and 70%. With the decline of the FEV_1 values in the range 50% to 35% and <35% (ie, COPD of higher severity) crude and adjusted HRs indicated no statistically significant excess of mortality risk. Data were limited to very few patients in the stratum of FEV_1 values over 70%, (ie, the higher forced expiratory volume being indicative of a better lung function and COPD of lower severity) for whom adjusted HRs could not be estimated.

10.5.1.5 Sensitivity Analysis by Cumulative Exposure (≤12 Months, >12 to 24 months, and >24 months)

To facilitate cross-classification of ever vs never use and current/recent/past vs never use with cumulative exposure, exposure analyses were stratified by duration of cumulative use by categories of ≤12 months, >12 to 24 months, and >24 months (Table 42). In GER, the mortality risk estimate was lower with cumulative exposure for >24 months compared with categories of shorter exposure duration and did not reach statistical significance. In SWE, no significantly elevated mortality risk was observed in any of the cumulative duration categories. In the US adjusted mortality risk was significantly elevated for all exposure duration categories, without a clear pattern observed.

Table 42 Sensitivity Analysis of 5-Year All-cause Mortality for Ever-Versus-Never Use of Roflumilast Stratified by ≤12 months, >12 to 24 months, and >24 months of Cumulative Exposure

All-cause mortality	GER[a]			SWE			US		
	≤12 months	>12 to 24 months	>24 months	≤12 months	>12 to 24 months	>24 months	≤12 months	>12 to 24 months	>24 months
Deaths (person-years)	2182 (23373)	489 (4823)	559 (6258)	1089 (8514)	169 (1544)	217 (2079)	3004 (22566)	683 (5427)	903 (6785)
N at risk	8775	3642	2724	3234	1171	880	9598	4171	3062
Crude HR (95% CI)	1.20 (1.14, 1.25)	1.26 (1.15, 1.38)	1.02 (0.94, 1.12)	1.16 (1.09, 1.24)	1.00 (0.86, 1.17)	0.98 (0.85, 1.12)	1.26 (1.21, 1.31)	1.21 (1.12, 1.31)	1.26 (1.17, 1.34)
Adjusted[b] HR (95% CI)	1.12 (1.07, 1.17)	1.23 (1.12, 1.35)	1.05 (0.96, 1.15)	0.99 (0.92, 1.06)	0.96 (0.82, 1.12)	0.94 (0.81, 1.08)	1.17 (1.12, 1.22)	1.12 (1.04, 1.21)	1.17 (1.10, 1.26)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country. Analysis stratified by different exposure definitions.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = Hazard ratio; PS = propensity score; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11i, Table 35 i1, 37 i1; Appendix 2.1 Table 29; Appendix 3.1 Table 29

10.5.1.6 Sensitivity Analysis of Current, Recent, and Past Exposure to Roflumilast Stratified by Cumulative Exposure (≤12 months, >12 to 24 months, and >24 months)

The mortality risk associated with current, recent, and past use of roflumilast versus never use was stratified by cumulative use ≤12 months, >12 to 24 months, and >24 months (Table 43). Overall, there were no consistent patterns of risk across the 3 countries in this analysis. No elevated risk was observed for current use of roflumilast for any of the durations of use, except for in the US for >24 months.

In GER, in line with the main analysis, during recent and past use, the crude and adjusted HRs increased with duration of use showing statistically significant differences versus those never exposed in all the cumulative exposure categories.

In SWE, adjusted HRs showed a statistically significant increase of mortality risk only during past use for each cumulative exposure category, and during recent use when cumulative exposure was >24 months, but not for lower cumulative exposure durations. However, the very small number of events and patient time at risk in the recent use stratum make any interpretation difficult.

In the US, all adjusted HRs showed a statistically significant increase of mortality risk for recent and past use for all exposure duration categories. As in the main analysis by use status, estimates of mortality risk associated with recent exposure status were numerically larger than estimates for current and past exposure status.

Table 43 Sensitivity Analysis of 5-Year All-cause Mortality Associated with Current, Recent, and Past Exposure to Roflumilast for ≤12 months, >12 to 24 months, and >24 months of Cumulative Exposure Versus Never Exposure

All-cause mortality	≤12 months				>12 to 24 months			>24 months		
	Never (ref.)	Current	Recent	Past	Current	Recent	Past	Current	Recent	Past
GER[a]										
Deaths (person-years)	12071 (160716)	503 (6053)	139 (1138)	1540 (16182)	106 (1097)	29 (197)	60 (396)	453 (5603)	33 (146)	73 (509)
N at risk	41718	8775	6331	5376	3642	1150	769	2724	1012	617
Crude HR (95% CI)	1 (ref.)	0.90 (0.82, 0.99)	1.49 (1.25, 1.76)	1.30 (1.24, 1.38)	1.00 (0.89, 1.13)	1.88 (1.30, 2.70)	2.02 (1.74, 2.35)	0.94 (0.85, 1.03)	2.75 (1.95, 3.87)	1.73 (1.38, 2.19)
Adjusted [b] HR (95% CI)	1 (ref.)	0.87 (0.79, 0.96)	1.39 (1.18, 1.66)	1.20 (1.14, 1.27)	1.00 (0.89, 1.13)	1.76 (1.22, 2.54)	1.84 (1.58, 2.14)	0.97 (0.88, 1.06)	2.60 (1.85, 3.67)	1.70 (1.35, 2.14)
SWE										
Deaths (person-years)	6,104 (57,594)	212 (2095)	50 (397)	827 (6022)	106 (1097)	3 (50)	60 (396)	188 (1,886)	9 (36)	20 (156)
N at risk	15776	3234	2263	2037	1,171	300	234	880	239	166
Crude HR (95% CI)	1 (ref.)	0.76 (0.66, 0.87)	1.00 (0.75, 1.32)	1.35 (1.25, 1.45)	0.88 (0.73, 1.07)	0.58 (0.19, 1.79)	1.44 (1.11, 1.86)	0.95 (0.82, 1.10)	2.43 (1.26, 4.68)	1.30 (0.84, 2.02)
Adjusted [b] HR (95% CI)	1 (ref.)	0.71 (0.61, 0.82)	0.86 (0.64, 1.14)	1.11 (1.03, 1.20)	0.83 (0.68, 1.01)	0.56 (0.18, 1.74)	1.40 (1.08, 1.81)	0.91 (0.78, 1.06)	2.44 (1.26, 4.70)	1.12 (0.72, 1.74)
US										
Deaths (person-years)	17,539 (171,688)	801 (6730)	210 (1153)	1,993 (14,682)	399 (3,863)	53 (203)	231 (1359)	744 (5,982)	52 (168)	107 (634)
N at risk	47151	9598	6533	5368	4171	1313	900	3062	1145	770
Crude HR (95% CI)	1	0.99 (0.92, 1.06)	1.62 (1.41, 1.86)	1.37 (1.30, 1.43)	0.99 (0.90, 1.10)	2.58 (1.97, 3.37)	1.67 (1.47, 1.91)	1.18 (1.10, 1.28)	3.02 (2.30, 3.97)	1.67 (1.38, 2.02)
Adjusted [b] HR (95% CI)	1	0.93 (0.87, 1.01)	1.52 (1.33, 1.75)	1.26 (1.20, 1.32)	0.94 (0.85, 1.04)	2.40 (1.83, 3.15)	1.45 (1.27, 1.65)	1.11 (1.03, 1.19)	2.88 (2.19, 3.78)	1.53 (1.26, 1.85)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; PS = propensity score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11i, Table 35 i2; Appendix 2.1 Table 30; Appendix 3.1 Table 30

10.5.1.7 Sensitivity Analysis Related to Testing Cox Proportional Hazards Assumptions: All-cause Mortality Stratified by Year of Follow-up

Tests of whether the proportional hazard assumption of the Cox regression model holds in all countries were conducted. Results indicated that this assumption did not hold throughout follow-up. To assess the impact of time on the mortality HRs, a model was built to include yearly strata of follow-up (Table 44).

Adjusted HRs did not show a consistent time-related pattern across countries. No statistically significant increase in mortality was observed across strata in SWE up to 3 years of follow up. In GER and the US, HRs were consistently increased across strata except in GER for ≤1 year of follow up where no significantly increased risk was observed.

Table 44 Sensitivity Analysis for Adjusted Hazard Ratio of 5-Year All-cause Mortality According to Follow-up Time Period Exposures for Ever-Versus-Never Use of Roflumilast

Follow-up time period from index date[b]	Adjusted[a] HR (95% CI) for all-cause mortality		
	GER	SWE	US
Never use (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Ever use: ≤1 year	0.91 (0.84, 0.99)	0.76 (0.68, 0.85)	1.03 (0.97, 1.10)
Ever use: >1 to 2 years	1.11 (1.02, 1.21)	1.06 (0.94, 1.19)	1.18 (1.10, 1.26)
Ever use: >2 to 3 years	1.16 (1.06, 1.27)	1.06 (0.93, 1.20)	1.21 (1.12, 1.30)
Ever use: >3 to 4 years	1.30 (1.18, 1.42)	1.16 (1.01, 1.33)	1.23 (1.14, 1.33)
Ever use: >4 to 5 years[c]	1.31 (1.20, 1.44)	1.02 (0.88, 1.19)	1.29 (1.19, 1.40)
Ever use: >5 years	1.30 (1.20, 1.40)	1.29 (1.15, 1.46)	1.16 (1.06, 1.25)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10) + follow-up time period since index date. The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

[b] Analyses were conducted utilizing a single model, where the ever exposure was stratified according to follow-up time period from the index date: ≤1 year, >1-2 years, >2-3 years, >3-4 years, >4-5 years, >5 years. The time scale in the model is time since CED.

[c] For GER this stratum is "Ever use: >4 years"

CED = cohort entry date; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; NA = not applicable; PS = propensity score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 38 b1; Appendix 2.1 Table 36; Appendix 3.1 Table 37

10.5.1.8 Sensitivity analysis of all-cause mortality according to cumulative exposure duration (patients censored after first discontinuation)

In a sensitivity analysis of mortality according to cumulative exposure duration of roflumilast versus never use in SWE and the US, patients were censored after their first discontinuation of roflumilast.

With censoring after first discontinuation, all adjusted HRs for each of the cumulative exposure categories in SWE and the US showed no significant increases in mortality risk with increasing cumulative exposure compared to the unexposed in SWE and the US (Table 45).

Table 45 Sensitivity Analysis of All-cause Mortality According to Cumulative Exposure Duration (<3, 3 to 12, >12 to 24 months, >24 months) of Roflumilast Versus Never Use in Which Patients Are Censored After First Discontinuation in Sweden and the United States

	All-cause mortality	Never (ref.)	<3 months	3 to 12 months	>12 to 24 months	>24 months
SWE	Deaths (person-years)	1582 (12680)	81 (604)	68 (793)	62 (667)	177 (1638)
	N at risk	15776	3234	1832	761	566
	Crude HR (95% CI)	1	0.63 (0.50, 0.80)	0.59 (0.46, 0.77)	0.78 (0.59, 1.03)	1.25 (1.02, 1.53)
	Adjusted[a] HR (95% CI)	1	0.59 (0.46, 0.74)	0.51 (0.40, 0.66)	0.66 (0.50, 0.87)	0.98 (0.80, 1.21)
US	Deaths (person-years)	4378 (35101)	240 (1751)	273 (2460)	212 (1913)	428 (3651)
	N at risk	47,151	9598	5058	2311	1513
	Crude HR (95% CI)	1	0.73 (0.63, 0.83)	0.86 (0.75, 0.98)	0.95 (0.82, 1.11)	1.15 (1.02, 1.30)
	Adjusted[a] HR (95% CI)	1	0.67 (0.58, 0.77)	0.76 (0.67, 0.87)	0.81 (0.70, 0.94)	0.95 (0.84, 1.08)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10) + follow-up time period since index date. The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

Note: Analysis was not conducted for GER.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 2.1 Table 40; Appendix 3.1 Table 42

10.5.1.9 Intention-to-treat Sensitivity Analysis of 5-year All-cause Mortality

To test for any attrition bias that might have been introduced with potentially informative censoring of never-use patients when starting roflumilast during follow-up, an ITT analysis was run in each study country (Table 46).

In all countries, the ITT analysis results were quite similar to the results of the main analyses.

Table 46 Intention-to-treat Sensitivity Analysis for 5-Year All-cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast Presented by Country

Use status	N at risk	PY	No of events	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
GER					
Never	35542	143990	10852	1 (ref.)	1 (ref.)
Ever	7373	29067	2673	1.17 (1.12, 1.22)	1.10 (1.06, 1.15)
SWE					
Never	12863	49596	5190	1 (ref.)	1 (ref.)
Ever	2626	9977	1168	1.09 (1.02, 1.16)	0.98 (0.92, 1.05)
US					
Never	39331	151587	15355	1 (ref.)	1 (ref.)
Ever	7961	29209	3692	1.23 (1.18, 1.27)	1.16 (1.11, 1.20)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity score; PY = person-years; ref. = reference; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 11h, Table 35h, Table 37h; Appendix 2.1 Table 37; Appendix 3.1 Table 38

10.5.1.10 HDPS Sensitivity Analysis of the Primary Outcome

Results of the HDPS matching are presented in Appendix 1 Table HDPS 1 to Table HDPS 6 for GER, Appendix 2.1 Table 31 to Table 35 for SWE, and Appendix 3.1 Table 31 to Table 36 for the US.

In the HDPS-matched patients, the mortality risk was consistently higher in the roflumilast-exposed cohort compared to the unexposed cohort in each country, with a statistically significantly elevated adjusted HR in GER and the US (Table 47). The adjusted HRs were, however, numerically lower than in the analyses using conventional PS matching.

Table 47 Mortality Rates, Crude and Adjusted Hazard Ratios of 5-Year All-Cause Mortality for Ever-Versus-Never Exposure to Roflumilast After HDPS Matching

5-year all-cause mortality	GER	SWE	US
Number of ever exposed (PY)	8651 (34026)	3123 (14208)	9566 (40515)
Number of never exposed (PY)	41047 (157177)	14205 (61844)	46499 (193858)
Number of events (ever exposed)	3158	6849	20731
Number of events (never exposed)	12173	1755	5296
Mortality rate[a] ever exposed (95% CI)	92.81 (89.60, 96.11)	110.75 (108.15, 113.40)	106.94 (105.49, 108.41)
Mortality rate[a] never exposed (95% CI)	77.45 (76.08, 78.84)	123.52 (117.88, 129.44)	130.72 (127.24, 134.29)
Crude HR (95% CI)	1.14 (1.10, 1.19)	1.03 (0.97, 1.09)	1.18 (1.15, 1.22)
Adjusted[b] HR (95% CI)	1.09 (1.05, 1.13)	0.95 (0.90, 1.01)	1.12 (1.08, 1.16)

[a] Mortality rate estimates per 1000 person-years at risk

[b] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; GER = Germany; HR = hazard ratio; PY = person-years; SWE = Sweden; US = United States

Source: Appendix 1 Table HDPS 7, Table HDPS 8, Table HDPS 9a; Appendix 2.1 Table 50; Appendix 3.1 Table 52

10.5.2 Exploratory Analyses

10.5.2.1 Subgroup Analysis by Presence or Absence of Asthma

As previously reported in the second and third interim reports, subgroup analyses of 5-year all-cause mortality in ever-versus-never use of roflumilast by presence or absence of asthma did not show any impact of asthma on the estimated mortality risk in SWE and only a small impact in GER while in the US, the adjusted HR estimate was lower in patients with asthma than those without asthma (Table 57).

10.5.2.2 Further adjustment of the Cox model with Unbalanced Covariates at 1 Year Before CED

Due to the residual imbalance between roflumilast treated and untreated cohorts noted at baseline after PS matching, a further attempt was made to adjust the HRs for imbalances in COPD markers of severity and morbidity seen at CED-1 in all countries. In the 5-year all-cause mortality of ever-versus-never use of roflumilast and in all the sensitivity analyses conducted by use status, cumulative use and time since discontinuation, further HR adjustments resulted in lowering the adjusted HRs in SWE and the US (Table 48), in relation to the main analysis (Table 26, Table 27, Table 28).

Table 48 Hazard Ratios of 5-Year All-cause Mortality for Different Exposure Categories of Roflumilast Use Further Adjusted for Imbalanced (Standardised Mean Difference >0.1) Covariates at 1 Year Before CED

All-cause mortality	Adjusted[a] HR (95% CI)		
	GER	SWE	US
Ever use			
Never	NR	1 (ref.)	1 (ref.)
Ever	NR	0.96 (0.90, 1.02)	1.13 (1.09, 1.17)
Cumulative duration			
Up to 3 months	NR	0.97 (0.88, 1.07)	1.13 (1.07, 1.19)
3 to 12 months	NR	0.97 (0.88, 1.05)	1.15 (1.09, 1.21)
More than 12 months	NR	0.92 (0.83, 1.03)	1.12 (1.06, 1.18)
Use status			
Current	NR	0.79 (0.72, 0.86)	0.97 (0.92, 1.01)
Recent	NR	0.91 (0.71, 1.17)	1.74 (1.55, 1.95)
Past	NR	1.09 (1.02, 1.18)	1.25 (1.19, 1.30)
Time since discontinuation			
Concurrent	NR	0.78 (0.71, 0.86)	0.96 (0.91, 1.01)
Up to 3 months (1-89 days)	NR	1.00 (0.82, 1.22)	1.65 (1.50, 1.81)
3 to 12 months	NR	1.02 (0.89, 1.17)	1.25 (1.15, 1.35)
More than 12 months	NR	1.12 (1.03, 1.22)	1.23 (1.17, 1.30)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10) + country specific unbalanced covariates at CED-1 (Figure 6 to Figure 3). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CED = cohort entry date; CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; NR= not reported; PS = propensity score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 2.1 Table 38; Appendix 3.1 Table 39

10.5.2.3 Analysis of Hospitalisations Surrounding Roflumilast Discontinuation

Since an increased mortality risk was found in association with the status "recent roflumilast use," ie, between the first 6 to 60 days following discontinuation of roflumilast, exploratory analyses were performed in all countries for patients who died in the recent use period investigating their health status with respect to hospitalisations for any cause and hospitalisations for respiratory disease (Table 49). These analyses could only be performed in the roflumilast-exposed cohort since the exposure status current, recent, past use could not be defined in the unexposed cohort (ie, never exposed). The number of patients with at least one hospitalisation in the roflumilast-exposed patients were evaluated a) in the recent use period before death, b) in the time period up to 55 days before the recent use period and/or c) in the time period 56 to 110 days before the recent use period. Since patients discontinue roflumilast intake 1 to 5 days before the recent use period, increasing percentages of patients with at least one hospitalisation in the time window ≤55 days before recent use might be considered as an indication of the deteriorating health status of a patient compared to the time window before,

ie, the time period 56 to 110 days before the recent use period. To allow comparisons of the frequency of patients with at least one hospitalisation between these 2 time windows (≤55 days before recent use and 56 to 110 days before recent use), only patients who could be observed for the entire period of 110 days were included in this analysis.

In all countries the frequency of patients with hospitalisations for any cause and of patients with respiratory disease-related hospitalisations increased from time window of 56 to 110 days to the time window of 55 days before start of the recent use. The percentage of patients with at least one all-cause hospitalisation increased from 50.0% to 68.4% in GER, from 33.3% to 60.4% in SWE and from 16.3% to 44.3% in the US. Similarly, the percentage of patients with at least 1 respiratory disease-related hospitalisation increased from 21.7% to 32.2% in GER, from 20.8% to 43.8% in SWE, and from 6.9% to 22.0% in the US in these 2 time windows. The high percentage of patients with at least one all-cause hospitalisation during any of the three time periods is remarkable: 89% in GER, 98% in SWE and 67% in the US which in itself may be related to changes in treatment. High percentages also apply to patients with at least one respiratory disease related hospitalisation during any of the three time periods, with 48% in GER, 71% in SWE and 32% in the US. Of note, many of the patients had hospitalisations not only during one of the time periods, but the sum of the patients with hospitalizations during the different time periods exceeded the number given in the last column: e.g. in GER for patients with all-cause hospitalizations 56+104+76=236 markedly exceeds the number of 135 patients given in the last column indicating that many patients were hospitalized not only during one time period.

These findings might indicate a deterioration in health status which might have triggered the discontinuation of roflumilast leading to the status of recent use and could also be related to the subsequently observed death (Table 49).

Table 49 Roflumilast-exposed patients Who Died During the Recent Use Period: Percentages of Patients with Hospitalisations for Any Cause and with Hospitalisations for Respiratory Diseases in Different Time Windows of Observation

	Observed during recent use period	Observed ≤55 days before recent use period	Observed 56-110 days before recent use period	Total
GER				
Exposed patients who died during recent use period	152	152	152	152
Patients with at least 1 hospitalisation for any cause (including respiratory diseases)	56 (36.84%)	104 (68.42%)	76 (50.00%)	135 (88.82%)
Patients with at least 1 respiratory disease-related hospitalisation	25 (16.45%)	49 (32.24%)	33 (21.71%)	73 (48.03%)
SWE				
Exposed patients who died during recent use period	48	48	48	48
Patients with at least 1 hospitalisation for any cause (including respiratory diseases)	32 (66.67%)	29 (60.42%)	16 (33.33%)	47 (97.92%)
Patients with at least 1 respiratory disease-related hospitalisation	18 (37.50%)	21 (43.75%)	10 (20.83%)	34 (70.83%)
US				
Exposed patients who died during recent use period	246	246	246	246
Patients with at least 1 hospitalisation for any cause (including respiratory diseases)	66 (26.83 %)	109 (44.31%)	40 (16.26%)	165 (67.07 %)
Patients with at least 1 respiratory disease-related hospitalisation	28 (11.38 %)	54 (21.95%)	17 (6.91%)	79 (32.11 %)

Note: patients may have experienced the respective events in multiple time intervals. This table includes only patients who were observed for the entire duration of 110 days (ie, before and during recent use).

GER = Germany; SWE = Sweden; US = United States.

Sources: Appendix 1 Table 27b; Appendix 2.1 Table 39; Appendix 3.1 Table 40

10.5.2.4 Sensitivity Analyses for Hospitalisation for Suicide Attempt (GER only)

A sensitivity analysis was conducted in GER exploring the risk of hospitalisation for suicide associated with current use of roflumilast. This analysis did not consider the main discharge diagnoses of poisonings, but it considered main and secondary hospital discharge diagnoses of X84.9! ("intentional self-harm"). This sensitivity analysis was only performed in GER, since code X84.9! is not available in SWE and the US as it is based on the German modification of the ICD-10 coding system although several other codes indicating suicide are available in SWE and the US that are not available in GER.

In this analysis in GER, only a few events were observed amongst exposed and unexposed patients, which resulted in estimates of crude HR of 1.14 (95% CI: 0.78, 1.67) for current use and 1.35 (95% CI: 0.49, 3.69) for recent use compared to never use (see Appendix 1, Table 39). Due to the small numbers of events, risk estimates are very unstable in this analysis and have wide CIs.

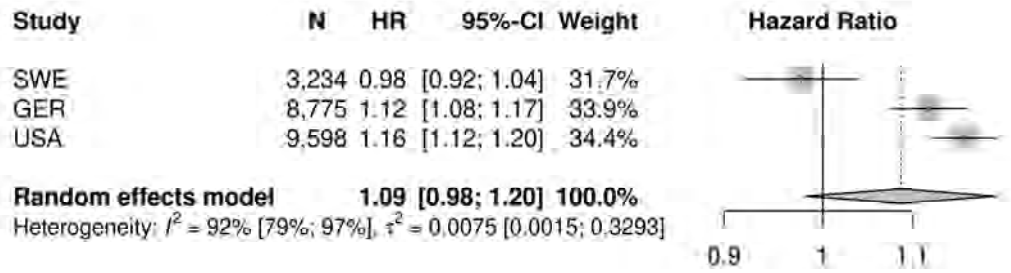
10.6 Meta-analysis

10.6.1 Primary Outcome

In the meta-analysis, considerable between-country heterogeneity of data from GER, SWE, and the US was observed (I^2=92%; Figure 14), with outputs from GER and US showing a slightly increased risk in 5-year all-cause mortality while SWE showed a non-significant beneficial effect. This heterogeneity might be due to the fact that in Sweden, due to the long data availability before CED, the variable "duration of COPD" was able to be included in the PS model, whereas this was not possible for GER and the US due to the limited data before CED. Since duration of COPD is an important marker of COPD severity, inclusion of this variable into the PS model presumably achieved better balance regarding COPD severity between the exposed and unexposed cohort in SWE. As a result, most mortality risk estimates were not increased in SWE, whereas mortality risk was increased in GER and the US possibly due to the limited balance of COPD severity between the exposed and unexposed.

Analyses by exposure categories (cumulative duration of use, current exposure) showed no consistent evidence of an increased risk of mortality across study countries (Figure 15).

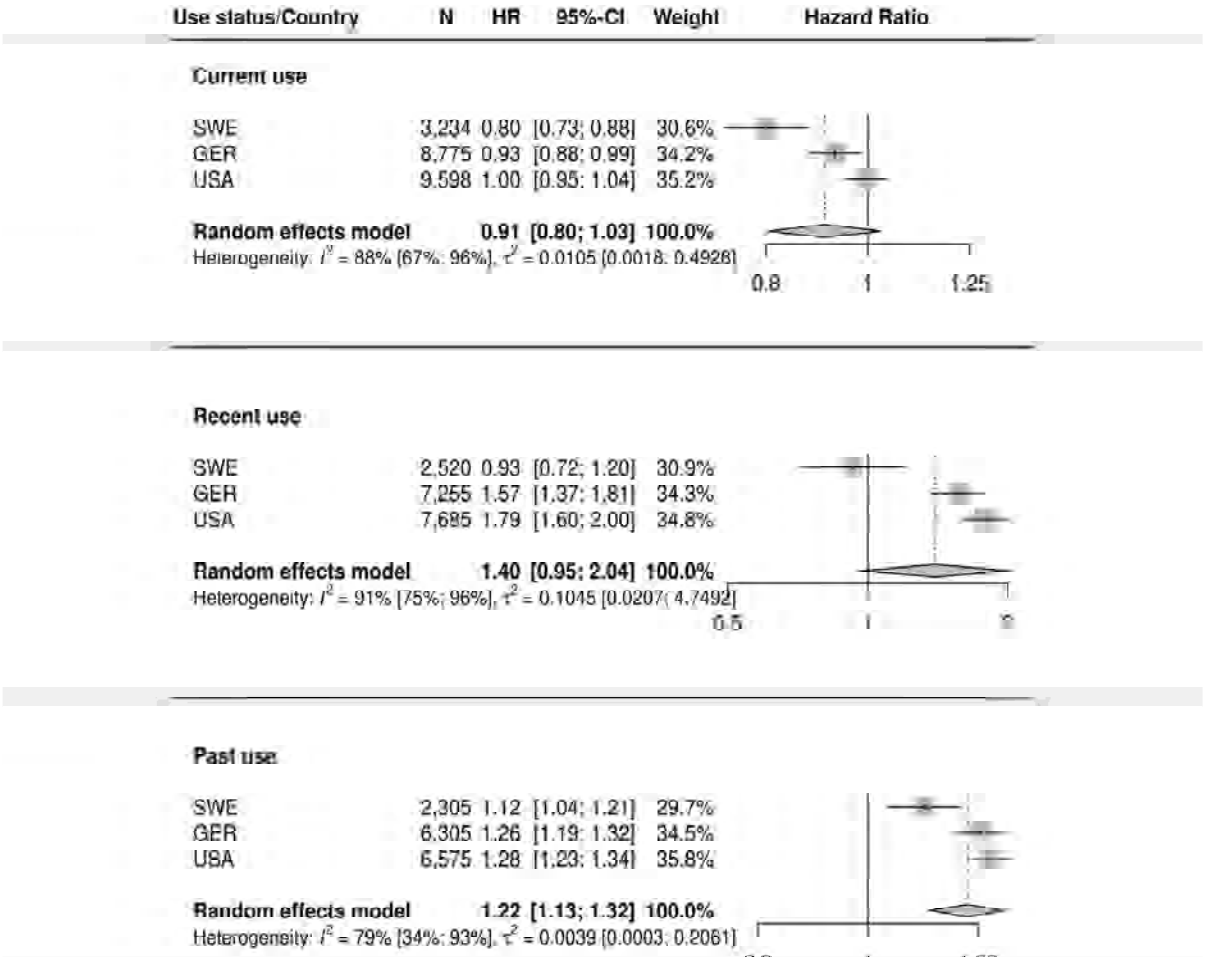
Figure 14 Meta-Analysis Showing the Adjusted Hazard Ratios for 5-Year All-Cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; HR = hazard ratio; GER = Germany; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 1

Figure 15 Meta-Analysis Showing the Adjusted Hazard Ratios for 5-Year All-Cause Mortality Associated with Use status (Current, Recent, and Past) Versus Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



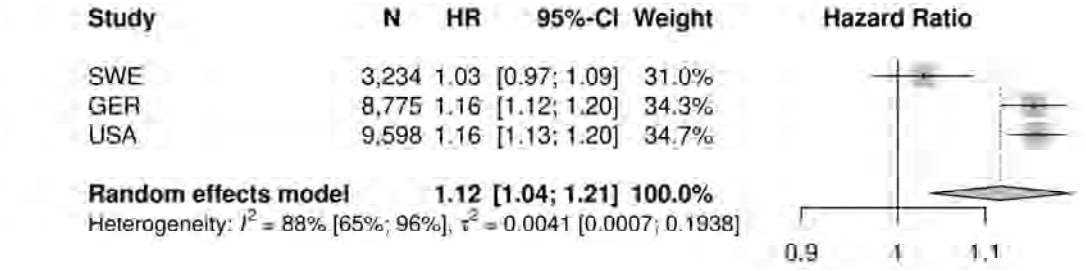
CI = confidence interval; HR = hazard ratio; GER = Germany; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 2

10.6.2 Secondary Outcomes

The meta-analysis showing the adjusted HRs for all-cause mortality with ever-versus-never exposure to roflumilast is shown in Figure 16; the adjusted HRs for hospitalisation for any cause is show in Figure 17; the adjusted HRs for major cardiovascular events leading to hospitalisation is shown in Figure 18; the adjusted HRs for respiratory disease-related hospitalisation is shown in Figure 19; the adjusted HRs for new diagnosis of malignant neoplasm is shown in Figure 20; and the 5-year all-cause mortality associated with ever-versus-never exposure for HDPS Matching is shown in Figure 21.

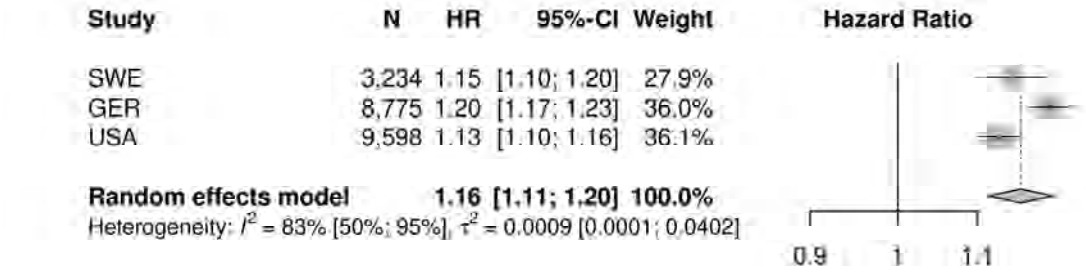
Figure 16 Meta-Analysis Showing the Adjusted Hazard Ratios for All-Cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 5

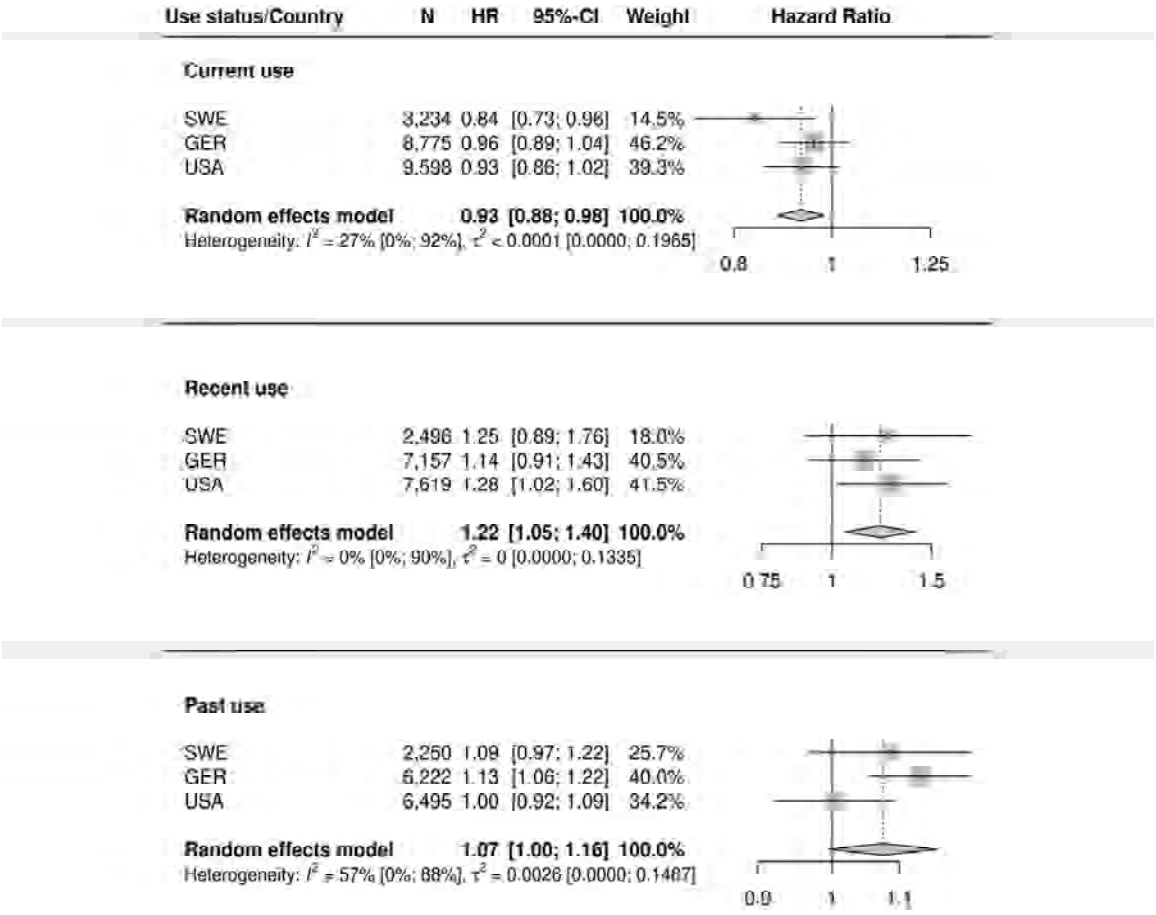
Figure 17 Meta-Analysis Showing the Adjusted Hazard Ratios for Hospitalisation for Any Cause Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 9

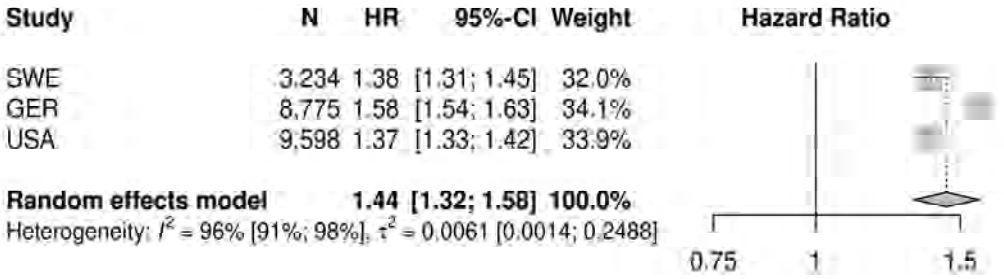
Figure 18 Meta-Analysis Showing the Adjusted Hazard Ratios for Major Cardiovascular Events Leading to Hospitalisation Associated with Use Status (Current, Recent, and Past) Versus Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 13

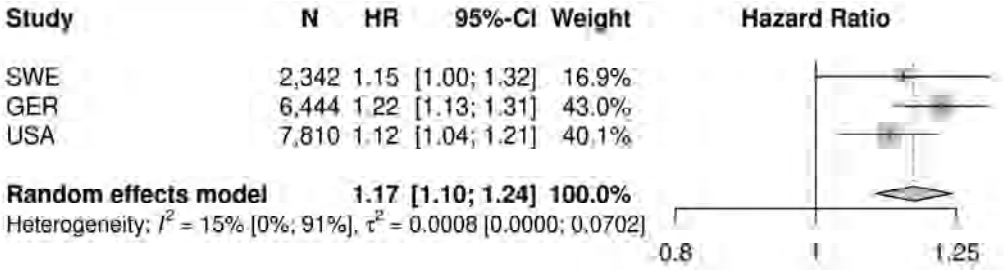
Figure 19 Meta-Analysis Showing the Adjusted Hazard Ratios for Respiratory Disease-related Hospitalisation Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 16

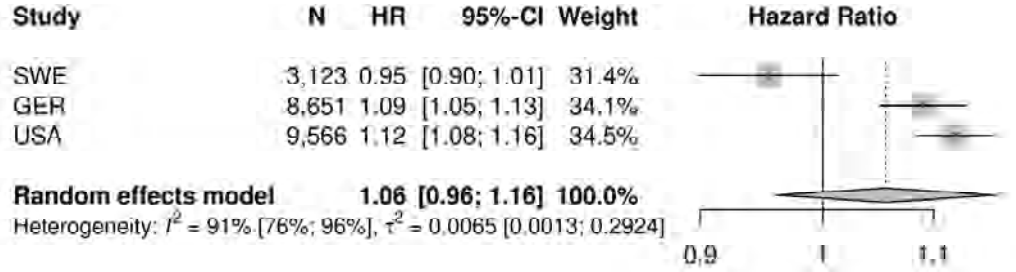
Figure 20 Meta-Analysis Showing the Adjusted Hazard Ratios for New Diagnosis of Malignant Neoplasm (Except Non-Melanoma Skin Cancer) Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 20

Figure 21 Meta-Analysis Showing Adjusted Hazard Ratios of 5- Year All-Cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) for HDPS Matching Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HDPS = high-dimensional propensity score; HR = hazard ratio; N = number of patients; SWE = Sweden; US = United States

Source: Meta-analysis, Figure 22

10.7 Adverse Events/Adverse Reactions (Not Applicable)

11. DISCUSSION

11.1 Key Results

This is the first long-term post-marketing observational study of the safety of roflumilast, following clinical trials which were of 12-month duration. The main objective of this study was to evaluate the long-term safety of roflumilast with the main analysis evaluating 5-year all-cause mortality in COPD patients. Secondary study outcomes included potential safety issues identified during the development programme of roflumilast. To this purpose, in 3 databases in GER, SWE, and the US study cohorts of COPD were identified in 2011, 2012, and 2013, roflumilast-treated patients were matched to roflumilast-untreated patients using PS methods. In response to the regulatory review and comments to the first interim report for this study, analysis using Norwegian registries was planned. However, due to delays with data access, the Norwegian results were not ready at the time of this report, and will be presented separately.

Based on the study duration, the potential follow-up for patients in the study was up to 6 years 5 months in GER, 7 years in SWE, and 6 years 7 months in the US. The average follow-up time in this report is in excess of 1545.51 days (4.2 years) in all countries (Table 18). In GER and the US, the sizes of the study populations are comparable, with 8775 and 9598 exposed patients and 41784 and 47151 unexposed patients, respectively included in the analyses (Table 11). The study cohort in SWE is smaller, with 3234 exposed and 15776 unexposed patients.

Of all roflumilast-exposed patients, 542, 15, and 43 patients had to be excluded, in GER, SWE, and the US, respectively, since no matching controls could be found. The unmatched roflumilast-exposed patients had higher COPD disease severity than matched roflumilast-

exposed patients, as reflected in the distribution of their PS values (Table 15; Section 10.1). The PS values for the unmatched roflumilast-exposed patients were all in the fifth quintile of the PS distribution in all 3 countries. As could be expected, the all-cause MRs in the unmatched roflumilast-exposed patients were higher than in the matched roflumilast-exposed patients (Table 16). Additional analyses conducted to further understand the unmatched roflumilast users compared to the matched roflumilast users included survival curves evaluating time to death. In all countries evaluated (GER, US, and SWE), the survival curves separate early with a lower probability of survival in the unmatched cohort. In GER, where the survival curves (distribution) were compared using log rank tests, the difference was statistically significant (p-value <0.0001). These results are consistent with the observation that the unmatched patients had the highest PS scores, and therefore more likely to have higher COPD severity than the matched cohort. Nonetheless, evidence from all study countries indicated that when matched patients with logit of PS >-2 were compared with all unmatched patients, only a small number of unmatched patients had PS values not represented by the matched exposed patients.

The PS matching within each annual cohort resulted in a similar PS distribution between the exposed and unexposed patients in all countries. However, despite PS matching, at cohort entry, more patients in the roflumilast-exposed cohort had high PS values, indicating higher COPD severity. Some variables in each country remained imbalanced according to the preset threshold for balance of 0.1 standardised difference. In addition, several variables had imbalances below this threshold, generally in the direction of higher severity in the roflumilast-exposed cohort. Furthermore, a descriptive analysis conducted in all countries showed that after matching at cohort entry, several PS variables assessed at 1 year before study entry exceeded the threshold of 0.1 standardised difference between treated and untreated patients, further demonstrating that the PS model and matching did not achieve an optimal balance and that a baseline imbalance of COPD severity markers was still present. In all 3 countries, standardised differences for PS variables related to COPD severity progressively increased during follow-up over the threshold of 0.1, indicating a growing deterioration of balance between roflumilast-exposed and unexposed patients.

While a plausible explanation for the observation of a deterioration in PS variables related to COPD severity over time may be a lack of roflumilast efficacy, evidence from well conducted and powered RCTs designed to evaluate efficacy up to 12 months do not support this explanation. The clinical efficacy of roflumilast in the treatment of moderate to very severe COPD has been well studied in a series of large mostly placebo-controlled clinical trials. Overall, 23 phase 2 to 4 studies were performed in the clinical development program to assess the efficacy (including exacerbation rate and lung function) of roflumilast compared to placebo. In particular, RESPOND and REACT were conducted to investigate whether roflumilast, on top of a fixed dose of LABAs and ICS in patients with severe COPD, could reduce the rate of moderate to severe exacerbations. These clinical studies demonstrated the efficacy of roflumilast use in reducing exacerbations.

Consistent with data presented in the previous interim reports for the primary outcome of 5-year all-cause mortality, crude MRRs and HRs were elevated for ever-versus-never exposure to roflumilast in each country. After adjustment for age, sex, the country-specific variables imbalanced after PS matching, and for markers of COPD severity and general

morbidity, in SWE there was no statistically significant difference in the 5-year mortality risk for ever-versus-never exposure to roflumilast, with an adjusted HR of 0.98 (95% CI: 0.92, 1.04) (Table 29). The adjusted HRs in GER (1.12 [95% CI: 1.08, 1.17]) and the US (1.16 [95% CI: 1.12, 1.20]) were reduced compared to the crude HRs (1.17 [95% CI: 1.13, 1.22] and 1.25 [95% CI: 1.21, 1.29], respectively). With further adjustment for covariates that were unbalanced (standardised mean difference >0.1) at 1 year before CED, the HRs for ever-versus-never use of roflumilast were further reduced to 0.96 (95% CI: 0.90, 1.02) in SWE and 1.13 (95% CI: 1.09, 1.17) in the US (Table 48).

Ever-versus-never exposure is a comparison of rather crude exposure categories, mixing not only current, recent, and past exposures, but also conflating different cumulative durations of exposure. Analyses by cumulative duration of exposure are, however, key to better understand the safety of roflumilast during long-term treatment. Previous reports analysed 5-year all-cause mortality by cumulative durations of <3 months, 3 to 12 months, and >12 months. A dichotomous split of cumulative duration ≤12 months and >12 months was also assessed. With the longer follow-up of patients included in this final report, analyses of ever-versus-never use of roflumilast were also performed with cumulative duration categories refined to ≤12 months, >12 to 24 months, and >24 months (Table 32). Across the countries, no consistent pattern of an elevated risk for any particular cumulative duration stratum was apparent (Table 32).

In SWE and the US, censoring of patients after first discontinuation of roflumilast (which more closely resembles the set-up of clinical trials) reduced the adjusted HRs in all cumulative exposure categories studied versus the unexposed (Table 45). For cumulative exposure durations >24 months, adjusted HRs were 0.98 (95% CI: 0.80, 1.21) in SWE and 0.95 (95% CI: 0.84, 1.08) in the US.

Additional adjustment for covariates unbalanced at 1 year before CE in the analysis using cumulative duration of <3 months, 3 to 12 months, and >12 months further reduced the adjusted HRs for cumulative exposure >12 months to statistically non-significant values in SWE (HR: 0.92; 95% CI: 0.83, 1.03) (Table 48). In the US, the HR for cumulative exposure >12 months was reduced, but remained statistically significant versus the unexposed (HR: 1.12; 95% CI: 1.06, 1.18); the analysis was not conducted in GER.

As with the lack of a consistent association of the risk of mortality by increasing roflumilast exposure duration, the stratified analyses by number of roflumilast dispensations did not reveal a consistent association between the risk of death and an increasing number of roflumilast dispensations (Table 54). The HR was significantly increased for ≥10 dispensations in GER but was reduced in SWE and the US, for the comparison of ≥10 dispensations of roflumilast versus never use. Overall, these results suggest that increased exposure to roflumilast is not associated with an increasing mortality risk.

In the analyses according to current, recent, and past versus never roflumilast use, adjusted HRs of 5-year mortality risk associated with current use were consistently the lowest in the analysis of use status and were also lower than the point estimates for ever-versus-never exposure from the main analysis. For the current category, adjusted HRs were 0.93 (95% CI: 0.88, 0.98) in GER, 0.80 (95% CI: 0.73, 0.88) in SWE, and 1.00 (95% CI: 0.95, 1.04) in the

US. On the other hand, statistically significant elevated estimates of adjusted HRs for mortality were observed in GER and the US during recent use and to a lesser extent during past use (Table 30). Concerning the increased risk in recent users, PRAC requested an analysis to further investigate their concern about misclassification of current use as recent use with respect to the increased mortality risk in recent users and provide "a sensitivity analysis indicating the time to on-set of death in the time window of recent use". Limitations to this sensitivity analysis are discussed in Section 11.2.

In GER and the US, the association of recent roflumilast use with an increased risk of 5-year mortality became more marked when current, recent, and past use of roflumilast were stratified by cumulative duration of exposure (Table 43). For current use of roflumilast, no elevated risk was observed for any of the durations of use, except for in the US in the stratum of most prolonged exposure duration of >24 months. For recent use, adjusted HRs reached statistical significance for each duration category in GER and the US and only for >24 months in SWE. These findings have to be interpreted given the imbalances of COPD severity observed at CED and their increasing divergence over follow-up time as discussed above and further below (Section 11.3). Moreover, the HR was reduced for ≥10 dispensations of roflumilast compared to never use which does not point to an increased risk for long-term use.

In SWE, the only of the countries where cause-of-death data was available for this study, mortality from COPD had the highest share of all deaths in each use category: the percentage of deaths due to COPD was 54.6% in current users, 54.4% in recent users, 51.9% in past users and 42.6% in never users. The higher proportion of COPD deaths in each of the roflumilast exposure categories compared with that in unexposed patients suggests that this higher mortality from COPD is independent of an effect of roflumilast and rather is due to differences in COPD severity between exposed and unexposed, in spite of the PS matching performed.

An analysis of 5-year all-cause mortality for ever-versus-never exposure to roflumilast stratified by PS quintiles was conducted, where the first quintile reflects less severe COPD and the fifth quintile more severe COPD. In all 3 countries, the adjusted HRs showed a clear trend with the highest HR in the lowest quintile and lowest HR in the highest PS quintile. The adjusted HRs in the fifth PS quintile was 0.90 (95% CI: 0.83, 0.97) in GER, 0.87 (95% CI: 0.77, 0.99) in SWE, and 1.01 (95% CI: 0.94, 1.08) in the US.

A further analysis conducted in GER on all-cause mortality for ever-versus-never exposure to roflumilast which was stratified by FEV_1 values supported these findings. Adjusted HRs in patients with the lowest FEV_1 values of <35% (HR 0.96; 95% CI: 0.90, 1.03) and second lowest FEV_1 values of ≥35% and <50% (HR 0.99; 95% CI: 0.87, 1.11) were not elevated, while the highest adjusted HR was seen in the stratum of less compromised respiratory function with FEV_1 ≥50% and <70% (HR 1.30; 95% CI: 0.97, 1.73). The small number of events in the stratum of FEV_1 >70% did not allow to estimate the adjusted HR.

Both these findings related to the 5-year mortality risks according to PS quintiles or FEV_1 values indicate that improved control of confounding appears to have been achieved for patients with higher COPD severity, while this was not the case for patients with lower COPD severity. This could be due to the fact that many markers of COPD severity available in the

data and used in this study apply only, or more closely, to higher COPD severity, eg, hospitalisations for COPD exacerbations, emergency room visits for COPD, oxygen use and others. A more detailed discussion of this limitation can be found in the "Limitations" section of this report.

In the HDPS-matched patients, the 5-year all-cause mortality risk was consistently higher in the roflumilast-exposed cohort compared to the unexposed cohort in each country, with a statistically significantly elevated HR in GER and the US (Table 47). The adjusted HRs were, however, numerically lower than in the analyses using conventional PS matching.

Overall, the different 5-year mortality risk estimates for different exposure categories between SWE (mostly no increased risks) and GER/US (often slightly increased risks) could be due to the fact that data availability before CED was limited to 1-2 years in GER and the US, whereas there was data available longer before CED in SWE. This made it possible to include the variable "duration of COPD" into the PS model in SWE. Since "duration of COPD" is an important marker of COPD severity, inclusion of this variable into the PS model presumably achieved better balance between the exposed and unexposed cohort with respect to COPD severity in SWE, possibly explaining some of the discrepancies in the results between SWE and GER/US.

The secondary outcomes were fully in line with the results presented in the previous interim reports (Table 35). In all countries, an elevated risk of hospitalisations for respiratory diseases was observed for current use of roflumilast compared to never use, with adjusted HRs of 1.57 (95% CI: 1.51, 1.63) for GER, 1.32 (95% CI: 1.24, 1.41) for SWE, and 1.33 (95% CI: 1.28, 1.39) for the US. An elevated risk of hospitalisations for respiratory diseases was also observed in association with recent and past use of roflumilast in all 3 countries. The fact that the risk estimates were similarly elevated also for recent and past use, ie, regardless of the timing of roflumilast use, indicates that this may not be an effect of roflumilast, but caused by the higher severity of COPD in the exposed patient cohort. An increased risk for current versus never roflumilast use was also observed for all-cause hospitalisations in all countries, although risk estimates were lower than for respiratory disease-related hospitalisations with adjusted HRs of 1.21 (95% CI: 1.18, 1.25) in GER, 1.13 (95% CI: 1.08, 1.20) in SWE, and 1.12 (95% CI: 1.09, 1.16) in the US.

Increased risks of new diagnosis of depression were observed for current versus never roflumilast use in all countries, with adjusted HRs of 1.58 (95% CI: 1.29, 1.93) in GER, 1.69 (95% CI: 0.64, 4.46) in SWE, and 1.36 (95% CI: 1.25, 1.48) in the US. For hospitalisations due to diarrhoea of non-infectious origin, the adjusted HRs were elevated in all 3 countries (GER (HR: 1.07; 95% CI; 0.71, 1.59), SWE (HR: 1.55; 95% CI: 1.08, 2.24) and US (HR: 1.24; 95% CI: 1.08, 1.42). The adjusted HRs for abnormal and unexplained weight loss were 2.49 (95% CI: 1.65, 3.76) in GER, 1.57 (95% CI: 0.88, 2.83) in SWE, and 1.76 (95% CI: 1.67, 1.86) in the US. The precision of many of these estimates was low due to the small number of events. These findings are in line with evidence described in previous interim reports and are consistent with the safety concerns identified in the roflumilast RCTs.

Linkage to a cancer registry, which can provide adequate data quality and clinical details, was only available in SWE (see also Section 11.2), while in GER and the US, identification of new

malignancies was based on claims data only. It is conceivable that this might result in under-ascertainment of malignancies: in the unexposed, crude incidence rates of malignant neoplasms (per 1000) were lower in GER (IR: 253.5 [95% CI: 245.4, 261.8]) and the US (IR: 257.1 [95% CI: 249.73, 265.70]) compared to SWE (IR: 295.8 [95% CI:280.75, 311.65]). Results from SWE should therefore be used preferentially for the interpretation of cancer data. In the analyses, ever exposure to roflumilast resulted in slightly elevated risk estimate for new diagnosis of malignant neoplasm for ever use of roflumilast when no latency period was applied (HR of 1.12 [95% CI: 1.00, 1.27]) or when latency periods of 1 year (HR of 1.15 [95% CI: 1.00, 1.32]) or 2 years (HR of 1.12 [95% CI: 0.95, 1.31) were applied (Table 37). Analyses for solid tumours showed no clear differences for diverse latency allowance (Table 38). Adjusted HRs were 1.09 (95% CI: 1.03, 1.15) in GER, 1.03 (95% CI: 0.94, 1.14) in SWE, and 1.04 (95% CI: 0.98, 1.11) in the US when no latency was accounted for and did not diverge substantially with 1 or 2 years of latency. Reduced HR were observed for the subgroups of haematopoietic cancers for ever-versus-never use of roflumilast; however, numbers of these cancers were very limited.

The meta-analysis showed substantial between-country heterogeneity for the primary study outcome, with increased HR for 5-year mortality in two countries (GER and the US) and largely no elevated risks, even some protective effects in SWE. Since this heterogeneity cannot be solved by statistical methods, the results are presented in this study report for completeness, but they are difficult to interpret.

11.2 Limitations

This study is subject to many of the limitations common to cohort database analyses including quality issues such as missing or incorrect data, and the fact that the data were not collected for research purposes. Potential confounding, especially confounding by COPD severity, remains the main concern in this study. PS matching was applied at CE to reduce the discrepancy between roflumilast treated and untreated patients with respect to COPD severity and other potential risk factors for mortality and morbidity. Several markers of COPD severity were incorporated in the PS model, but despite these efforts - imbalances remained after PS matching, giving rise to residual confounding by COPD severity. Adjustment for markers of COPD severity in the Cox proportional hazards regression models eliminated the apparent association of ever use of roflumilast with all-cause mortality in SWE. A statistically significant association was still observed in the GER and the US analyses; however, risk estimates were reduced pointing to reduction of residual confounding.

The imperfect balance achieved at baseline was further illustrated by the analysis of markers of COPD severity at 1 year before cohort entry, suggesting that the covariate data from baseline and the previous year used in the PS model construction were not sufficient to capture pre-CED differences between treated and untreated cohorts. In fact, the assessment of balance of variables at CED-1 itself had some limitations as information was not available for all patients for all countries. Even though matching by PS at CE was conducted, standardised differences between treated and untreated cohorts for a number of PS variables related to COPD severity were still above the threshold of 0.1 when measured 1 year before CE indicating imperfect balance achieved at cohort entry. Besides, for many PS variables related to COPD severity the standardised differences were below but close to the 0.1 threshold value,

which, taken together, will impact on differences in COPD severity. These findings highlight the challenges of achieving a complete balance between treated and untreated cohorts with the data available in electronic healthcare databases, when confounding by disease severity is of major concern as in this study.

In response to the PRAC request during assessment of interim report 2, a high-dimensional propensity score approach was used to improve covariate balance and increase comparability of the exposed and unexposed cohorts. The HDPS aimed to empirically identify candidate covariates that may collectively be proxies for unobserved confounding of the outcome, particularly aiming to address confounding by indication, wherein more severe COPD patients are more likely to be prescribed roflumilast, and are also more likely to develop the outcomes of interest. However, after HDPS matching, there were only slight differences in number of patients compared with the PS matching.

PS matching of roflumilast treated and untreated patients was applied within the cohort of each individual year of study entry (2011, 2012, and 2013). However, in a long-term follow-up study such as this one, where patients could contribute to the analyses up to 7 years person time, the balance - though incomplete - that was achieved at CE between treated and untreated patients often tends to diverge over time, and strong evidence of this was found in this study. An increasing imbalance of variables related to COPD severity between roflumilast treated and untreated populations was observed when the baseline variables were reassessed at 1 to 5 years of follow-up in all countries. With the average follow-up time of at least 4.28 years, it is expected that the risks for roflumilast exposure will increase as the observation time extends, since the growing imbalances during follow-up will increase the magnitude of confounding by COPD severity. This is also described as time-dependent confounding.

As a limitation in all databases, information on clinical characteristics of the COPD patients (eg, magnitude of dyspnoea) or actual values from clinical investigations, eg, lung function tests were not available, which represents a major weakness of the data. In GER, results in about 79% of exposed and matched unexposed patients with respect to the FEV_1 were available due to the fact that in GER, FEV_1 categories can be coded by a 5-digit ICD-10 code of the German modification of the ICD-10 coding system; however, actual exact values for the forced vital capacity were lacking. Additionally, these FEV_1 values coded in GER were assessed at varying time points before baseline and may have changed over time, and the reason for performing a lung function test is also unknown. Clinical characteristics and lung function tests are particularly important when patients suffer from lower COPD severity since many markers of COPD severity available in the data and used in this study apply only, or more closely, to higher COPD severity, eg, hospitalisations for COPD exacerbations, emergency room visits for COPD, oxygen use and others. The lack of information on clinical characteristics and lung function tests is therefore a particular limitation in the analysis of patients with lower COPD severity and quite expectedly, results of this study indicate that residual confounding was stronger in this subgroup of patients, while it was lessened in the subgroup of patients with more severe COPD where the adjustment variables for COPD severity used in this study were more relevant. In line with this, in the most severe subgroup of patients defined by the highest PS quintile, no increased risk of mortality for ever-versus-never exposure was observed in GER and SWE. This was not as clearly the case in the US,

suggesting that other markers of COPD severity should be adjusted for in the US. In an attempt to address this limitation, US specific variables were included in the Cox regression hazard model: number of hospitalisations for COPD in the 30 days before CED, number of emergency room visits in the 30 days before CED, and number of outpatient physician office visits for COPD in the 30 days before CED.

The GER data on 5-year all-cause MR, stratified by FEV_1, further support this argument and interpretation. Since FEV_1 values are mostly recorded in a hospital, it can be argued that patients with unspecified FEV_1 values are possibly those at lowest COPD severity, ie, those who were not hospitalised for their COPD. Indeed, an analysis of the distribution of PS quintiles across the FEV_1 strata confirmed that approximately 70% of patients in the first PS quintile (indicating the lowest COPD severity) were in the stratum of unspecified FEV_1 value (Table 55). A significantly elevated mortality risk was observed for patients in this stratum and in patients in the FEV_1 stratum 50% to 70%, whereas in the more severe FEV_1 strata, no elevated risks were observed.

In all databases of this study, additional relevant data were not available and could not be applied in the analyses. For instance, in GER, oxygen use as a marker for very high COPD severity was not available and outpatient diagnostic information in the GER database relates only to the quarter of a year, so that no exact date for outpatient diagnoses in GER was available. All secondary outcomes in GER were therefore based on hospitalisations to ensure availability of an exact date of the event (and ensuring that the exposure preceded the outcome), although for some secondary outcomes also outpatient diagnoses would have been desirable, since they are often treated in the outpatient setting, eg, new diagnosis of depression, unexplained weight loss, diarrhoea and others. In SWE, information was lacking on diagnoses made in primary care and medication had to be used as surrogate information, which is often less specific. The coding system in the US database did not allow a full characterisation of the specific reason for hospitalisation related to respiratory diseases (see Core SAP Section 9.3 and US SAP Addendum Table 4). Information on lifestyle variables as eg, exercise, diet was not available in any of the databases. This also applied to other conditions which may be available but are not generally systematically coded, as eg, obesity, which may then have resulted in misclassification since it was assumed that no obesity was present when it was not coded. No quality of life questionnaires were included in the assessments. Several risk factors for secondary outcomes, eg, related to all-cause hospitalisations, depression, or others such as overall morbidity and frailty, or mental state (depression, suicidal ideation), cannot be measured adequately in claims databases, leading to possible residual or unmeasured confounding also for the secondary outcomes.

In the PS matched, adjusted Cox models, when the current roflumilast use cohort was compared with the never use cohort, there was no increase in mortality risk in SWE, GER, and US. In GER and SWE, the results indicated a significantly protective effect. However, in comparing the recent use cohort with the never use cohort, there was a statistically significant increase in mortality risk for GER and US, which was not observed in SWE. While these results may be explained by the study design limitations of this study (ie, exposure could be classified as current, recent, and past use in the roflumilast group but a similar classification could not be performed for the unexposed group due to an absence of an active comparator. During review of the third interim report, PRAC indicated that the increased 5-year mortality

risk observed for recent use could in fact be related to current use, ie, whether the mortality risk observed in the current use might be misclassified as recent use. Based on this concern, PRAC requested that a "sensitivity analysis indicating the time to on-set of death in the time window of recent use" be conducted, presumably to detect events where the date of death closely followed discontinuation of roflumilast which might support the concern about misclassification. In this sensitivity analysis, the median (IQR) time to death in the "recent use" exposure stratum was 27 (12 to 40) days in GER, 22 (9 to 38) days in US and 30 (12 to 42) in SWE, which may indicate a uniform distribution of deaths during the specified time period. While this sensitivity analysis, has been conducted, the limitation of the uncertainty around drug exposure should be noted. In all four electronic healthcare databases, the start and end dates of drug intake are unknown and the duration of drug intake is calculated based on the number of dispensed drugs. For any drug dispensation, it is possible that drug intake ends early during the period dispensed medication is planned to cover. It is also possible that drug intake ends in the later period the dispensed medication is planned to cover. All of these factors lead to some uncertainty in ascertaining the drug exposure period as current vs recent.

A major limitation in the study databases is the lack of (GER) or limited (SWE, US) data on smoking, an important and strong risk factor for mortality and many other health outcomes. Coding for tobacco use in claims databases is likely to under-ascertain smoking to a large extent (Desai 2016). This is also the case in this study. In SWE and the US, available smoking information was included in the PS score to achieve balance on this variable in roflumilast exposed and unexposed patients. However, smoking data were very limited, eg, in SWE the ICD codes for identification of smokers, allowed to characterise as current or former smokers only approximately 10% of the study population, whereas in roflumilast RCTs, current and former smokers constituted 100% of the COPD study population (Martinez 2015; Martinez 2016). Besides under-ascertainment of smoking, ICD codes do also not distinguish between current and historical smoking habits, nor do they provide data on the cumulative amount smoked such as pack-years. Since smokers among COPD patients have a higher risk of COPD exacerbations (Au 2009) and roflumilast is licensed in patients with frequent exacerbations, it is quite conceivable that there are more and/or heavier smokers among the roflumilast-exposed patients, which would impact on mortality and the risk of (solid) cancers, in particular lung cancer. Data in SWE showed that of the solid tumours, about 31.9% were neoplasms of the bronchus and lung and about 28.6% affected the digestive organs, both of which are frequently related to smoking. Although the association between smoking and colorectal cancer has been controversial, recent meta-analyses have demonstrated that a consistent association exists between smoking and the risk of colorectal cancer with a significant relationship between duration of smoking and rectal cancer incidence (Larsen 2009; Liang 2009; Tsoi 2009). Tobacco smoking is also one of the main risk factors for gastric cancer (Ferro 2018). Therefore, lack of robust data on smoking in this study results in the strong possibility of unmeasured confounding for the primary outcome and for the secondary outcome of new malignancies.

There was also no information on whether a patient had actually used the roflumilast medication that was dispensed; however, given that patients were severely diseased it might be assumed that this was mostly the case for the COPD medications. Furthermore, there was no ability to confirm medication compliance with the prescribed schedule. Deviation from the expected treatment dose or lack of adherence to the prescribed treatment can all lead to

apparent treatment gaps in exposure, which do not necessarily coincide with treatment discontinuation in reality. To address this concern, the exposure period was prospectively extended by 50% of the amount of the previous prescription when there was no dispensation of roflumilast covering the day after the calculated end of the supply ("gap extension"). Sensitivity analyses were conducted in all countries by extending the exposure period instead by 100% or reducing it to 0% of the amount of the previous roflumilast dispensation. In GER and SWE, HR estimates were comparable to those observed in the main analysis of all-cause mortality associated with current, recent, and past use of roflumilast. More fluctuations were observed in the US data though no specific pattern could be noted. Overall, the sensitivity analyses supported the assumptions made in the exposure definitions adopted for this study.

Cancer data in SWE are based on clinical data from a well-established cancer registry that dates back to 1958. Cancer data in GER and in the US are based on claims data cancer diagnoses. No morphological confirmation of diagnosis is therefore available in these 2 countries. Given the nature of claims data, it is not possible to establish if the first cancer diagnosis seen after the cancer-free baseline and latency period is in fact a first diagnosis. In both countries only a very short lookback period was applied (in the US until January 2009, in GER only 1 year for each annual cohort in the analysis with the additional latency periods of 1 and 2 years). Therefore, misclassification of existing cancers as incident cancers may happen, particularly for cancers with longer survival. Considerable misclassification has been shown with short lookback periods in a recent study using claims data (Czwikla 2017). Further, the definition of cancer diagnoses did not address coding of cancer as "rule-out diagnosis" since no confirmatory cancer code or event was required. The misclassification of prevalent as incident cancers would be expected to result in higher crude IRs of (incident) cancers in GER and the US compared to SWE. However, this was not the case. since the crude incidence rate of malignancies was actually lower in GER and the US compared to SWE (Table 24) which does not indicate substantial misclassification.

A further limitation is that the current report does not include the planned analyses for NOR. During assessment of the third interim report, PRAC requested that results from Norway be presented in the final report. AstraZeneca submitted variations for extension of the final study report submission due date in order to complete the additional analysis requested by the EMA, including the use of data from Norway. AstraZeneca received agreement from the EMA to submit the final study report on 31 December 2022. In September 2022, AstraZeneca contacted EMA regarding challenges with obtaining access to the Norwegian data and the risk of the delay affecting AstraZeneca's ability to meet the final CSR submission timeline of 31 December 2022. In response the EMA advised that the timeline for final CSR submission in December 2022 be maintained, and if outputs from the Norwegian data were still unavailable or contained serious errors at that time, they should be omitted from the final CSR. However, the EMA advised that if the Norwegian outputs did become available during the assessment procedure, they would welcome its submission.

11.3 Interpretation

Small differences in the PS distribution after PS matching at CE between cohorts indicating that exposed patients still have more severe COPD than unexposed patients were observed in previous interim reports and were confirmed in these analyses. New additional analyses in all

countries presented in this report show that matching exposed and unexposed patients on the PS attenuated the differences in COPD severity observed at cohort entry; however, this balance was incomplete since after matching, several variables remained imbalanced not only at baseline but also assessed using data at one year before cohort entry. This report also includes an illustration of the partial loss of balance over time during follow-up when the distribution of PS matching variables was evaluated in the exposed and unexposed patients at 1 to 5 years after study entry in all countries. Balance particularly deteriorated for variables related to COPD severity. The increasing deterioration of balance related to COPD severity will result in confounded estimates related to longer cumulative exposure, since follow-up time and cumulative roflumilast exposure are closely interlinked. This could be a reason for the increased risks observed in stratified analyses of current, recent, or past use stratified by longer cumulative exposure categories.

It was postulated that the informative censoring of switchers that move from the never to the ever roflumilast exposed status, leading to the depletion over time of the more severe COPD patients from the unexposed cohort, could be a contributing factor to the imbalance observed over time. However, the intention to treat analysis presented in this report whereby all individuals from the unexposed group remained for assessment as unexposed even upon roflumilast initiation until the end of follow-up (ie, patients switching from unexposed to exposed were still accounted for as unexposed in the analysis) suggests that switchers might contribute only marginally if at all to this phenomenon. It is more likely that because of the nature of the drug under investigation, as a last line treatment in a therapeutic area where no alternative currently exists, most residual confounding will tend to be in the direction of higher COPD severity in the roflumilast-treated patients. Based on this observation, it can be expected that increasing risk estimates for roflumilast during follow-up might be observed. In such a context, even the best analytical methods established for observational research may be unable to completely eliminate this structural confounding by indication. This limitation is to be considered in combination with the intrinsic limitation of data in cohort analyses of electronic healthcare records and has to be taken into account in the interpretation of the analyses, including the analyses of cumulative exposure duration.

The crude HRs for the primary (and secondary) outcomes of this study are therefore considered to be confounded by differences in COPD severity between exposed and unexposed patients. In line with this, the estimated mortality risk was generally lower in all countries when the Cox proportional hazard regression model adjusted HRs for variables imbalanced after PS matching and for several identified markers of COPD severity and overall morbidity. In SWE, such adjustment resulted in non-significant HR estimates, while still statistically significant but lower risk estimates were observed in GER and the US. Adjustment for covariates related to COPD severity that remained imbalanced at 1 year before study entry further reduced the HR estimates for all-cause mortality in all exposed versus unexposed comparisons, thus confirming the issue of residual confounding by indication that the available data and modelling has difficulties to capture. Evidence described in this report further indicates that imbalances in COPD severity between exposed and unexposed at baseline further increased during follow-up, giving rise to increasing confounding by indication with longer follow-up. The analyses of mortality risk in ever versus never roflumilast use, stratified by cumulative duration (hence duration of follow-up), should be interpreted in this context.

Stratified analyses of the risk of all-cause mortality by using PS quintiles as a marker of COPD severity showed that the risk of death for roflumilast-treated patients was (more) elevated in the subgroup(s) with lower COPD severity (ie, in the subgroups defined by lower PS quintiles). This was clearly evident in GER and SWE, with similar but less consistent and weaker estimates in the US (Table 34). As discussed earlier in Section 11.2, such results had been anticipated, as they reflect an established limitation of database studies. In claims data COPD severity has to be approximated largely by variables such as COPD exacerbations or hospitalisations, which are related to more severe COPD, whereas other variables to ascertain COPD severity in patients with less severe COPD, eg, clinical characteristics, symptoms, or results of lung function tests are not available in the databases, leading to incomplete adjustment for COPD severity and overall, more confounded results in the subgroups with lower COPD severity. Since roflumilast is indicated for patients with severe COPD, the mere fact that the physician prescribed roflumilast may indicate more severe COPD in exposed patients. These subtle differences between exposed and unexposed patients particularly concerning patients with lower COPD severity could not be fully ascertained with the data available but are indicated by the higher risk estimates for roflumilast in the patients with lower COPD severity likely related to residual confounding by COPD severity. This hypothesis is further confirmed by the GER analysis of all-cause mortality stratified by FEV_1 values, whereby FEV_1 values are considered as markers of COPD severity. This analysis shows a numerically elevated mortality risk for roflumilast only in the less severe FEV_1 stratum (FEV_1 between 50% and 70%) and a statistically significant association between ever-versus-never use in the stratum where FEV_1 values were not available, which is assumed to include mostly non-hospitalised patients, presumed to experience lower COPD severity. In contrast, the HR estimates were below 1 and statistically significant association of all-cause mortality with ever-versus-never exposure with roflumilast was not observed in the strata for the lowest FEV_1 values (between 35% and 50% and less than 35%), which consisted of patients with more severe COPD. Further support for the hypothesis of greater confounding by COPD severity when comparing mortality in strata of less severe COPD derives from the findings of the stratified analyses by PS quintiles in the US. This analysis did not show as clear a distinction on mortality risk across PS quintiles, as observed in GER and SWE. The weaker estimates observed in the US data might reflect the different indications for roflumilast between the EU and the US (EU: severe COPD [FEV_1 post-bronchodilator less than 50% predicted] with a history of frequent exacerbations; US: severe COPD and a history of exacerbations) which might lead the patient population in the US to differ (ie, suffer from less severe COPD) as compared to the patient populations in GER and SWE. In line with this, among the number of hospitalisations for respiratory diseases, the percentage of hospitalisations due to COPD was lowest in the US in comparison to the other two countries (Table 25). Variations across countries linked to the diversity in the healthcare delivery systems, overall database structures and content, and coding practices, including a distinct US coding system for hospitalisation as discussed earlier, should also be accounted for in the interpretation of these results.

Further evidence on the potential for residual confounding derives from the distribution of PS variables after matching at CE and at 1 to 5 years of follow-up. In all countries there was evidence that the standardised differences between exposed and unexposed patients for some variables related to COPD medications and hospitalisations were imbalanced, and these differences increased with the increase of follow-up. As a result, imbalance in COPD severity

between roflumilast treated and untreated COPD patients increased over time. This observation is particularly relevant in the interpretation of analyses that directly or indirectly imply a prolonged follow-up time. For instance, the interpretation of the analysis on mortality in association with a cumulative roflumilast exposure duration of >12 to 24 months and >24 months should account for this time dependent confounding that the Cox regression hazard model might not be able to adjust for.

The main aim of this study was to assess the 5-year risk of mortality associated with long-term use of roflumilast, in order to complement the RCT data, which are limited to 12 months of treatment. The results in this report extended the observation period provided in previous reports showing that increasing cumulative exposure to roflumilast is not associated with an increasing mortality risk. Any marginal risk elevation observed for up to 12 months of cumulative use in GER and the US is inconsistent with the results of placebo-controlled RCTs, where mortality events were similar in the roflumilast and placebo exposed patients during a treatment period of 52 weeks (Martinez 2015, Martinez 2016, Calverley 2009). For instance, the adjusted HR of 1.18 (95% CI: 1.11, 1.26) observed in GER for cumulative use from 3 to 12 months is not aligned with clinical trial evidence and rather suggests that an elevated risk in this order of magnitude is likely due to residual confounding. Similarly, it can be postulated that increasing time-dependent confounding deriving from the prolonged follow-up (and accompanying deterioration of balance) may explain excess mortality risks observed in GER and the US with cumulative uses between >12 to 24 months or longer. Of note, no increased HR in 5-year mortality were observed for the cumulative roflumilast exposure categories in SWE, neither for more than 12 months of exposure nor for more than 24 months (Table 32).

In GER and SWE, current use of roflumilast was not associated with a statistically significant increase of HR for 5-year mortality in any strata of cumulative use up to 24 months or for more than 24 months of exposure duration (Table 43). In the US, no increased HR in mortality were observed for current use of roflumilast up to 24 months. The small increase in HR for more than 24 months is assumed to be due to deterioration of balance with longer follow-up as discussed above. These key results provide reassurance for the main study question of whether long-term use of roflumilast might be associated with an increased HR in mortality.

In contrast, findings of all-cause mortality related to timing of roflumilast use (ie, current, recent, or past use) without defining use status in different cumulative use categories remain difficult to interpret due to lack of homogeneity in cumulative duration of roflumilast use in these categories: current (or recent or past use) might be related to a cumulative use ranging from a few days to several years. These categories therefore do not offer much insight into the study question of the long-term safety of roflumilast with respect to all-cause mortality. Nonetheless, the mortality risk increase observed during recent use, especially when associated with prolonged cumulative use of roflumilast may raise concerns and deserves some further consideration. An inherent limitation of the “recent use” category is the small person-time compared to the “past” and “current use” categories, which suggests that all estimates for these categories should be interpreted with caution. The risk in the time window of recent use is usually investigated to evaluate a rebound effect of a drug, ie, an elevated risk during recent use might indicate a rebound effect. However, in a clinical study, where patients were randomised to treatment and closely monitored, withdrawal of roflumilast after 12 weeks

treatment showed no evidence of a rebound effect, as measured by FEV_1 (Rabe 2011). An increase of risk associated with recent use of medicines is a recurrent observation in pharmacoepidemiology and is likely to depend on the events surrounding the time of drug discontinuation. Since the reasons for discontinuation are not available in the databases of this study, an attempt was made to understand key events in roflumilast-exposed patients dying during the recent use period that surround the time of discontinuation before recent use. In line with preliminary evidence generated in GER for the third interim report, this report describes in all study countries the percentage of patients with hospitalisation for any cause and with hospitalisation for respiratory disease in the 55 days preceding the discontinuation of roflumilast leading to the status of recent use, and in the earlier period of 56 to 110 days before recent use status. The data indicate that consistently across countries in the 55 days preceding discontinuation the percentage of patients with a hospitalisation for any cause and related to a respiratory disease was higher than in the earlier period of 56 to 110 days before discontinuation. These findings indicate that a substantial percentage of roflumilast-exposed patients dying during recent use experienced severe medical conditions requiring hospital care before discontinuation which may have led to the decision to end the roflumilast therapy. When the health status of a patient markedly deteriorates, medication not deemed indispensable to life (eg, roflumilast) may be discontinued not to burden the patient with too many drugs. The subsequently observed death as a consequence of the patient's poor health status which at the same time led to discontinuation of the drug (eg, roflumilast) will appear as increased risk in the recent use period. It is noteworthy that the patients' deteriorating health status could only be described in the roflumilast exposed cohort, while the health status of the unexposed cohort could not be observed due to the lack of an active comparator that would enable the definition of recent and past use in the roflumilast unexposed cohort. This analysis indicates that during the time period of discontinuation of roflumilast a deterioration in the exposed patient's health status may have taken place. Similar circumstances could not be equally determined in the untreated population, which makes the comparison of recent (and past) use with never use of roflumilast problematic. In the new analysis requested by PRAC, the time to death appeared quite uniformly distributed in the recent exposure period; however, limitations of this analysis need to be taken into account.

The lack of an active comparator for which a discontinuation time point could be equally defined as for roflumilast is indeed a major challenge in this study. These circumstances are likely to make the transition from current to recent (and subsequently past) use of roflumilast an informative event, associated with worsening of COPD severity or overall health status of the patients, and potentially increasing mortality risk, which might produce an apparent increase in risk for recent use when similar deterioration cannot be captured in the comparison population of untreated patients. This hypothesis was evaluated (and confirmed) in an analysis of the 1-year roflumilast RCT data that were completed in the context of the product clinical development (Martinez 2015; Martinez 2016). The analyses, presented in Appendix 7, were conducted with the purpose of evaluating all-cause mortality in a setting where it was feasible to define current, recent, and past use in both the roflumilast treated cohort and the untreated comparator (placebo) cohort. In line with the findings of this report the findings from the RCT setting confirmed the absence of an increased mortality risk during 1 year of follow-up when comparing ever-versus-never users of roflumilast, with HRs close to 1 and not statistically significant. Similarly, the HR estimates did not indicate any excess mortality associated with current, recent, or past use of roflumilast when exposure status was evaluated as current,

recent, and past use in both the roflumilast and the placebo cohorts. However, HRs were numerically elevated particularly for recent use, when the exposure status categories current, recent, and past use were only applied to the roflumilast treated population but not to the placebo population (ie, exposure status in the comparator group was maintained as never use to mimic the comparisons in this PASS). These findings illustrate the importance to subdivide exposure also in the comparator cohort into current, recent, and past use, since the risk in the comparator cohort is not constant over time. Where this is not possible as, for example, in this PASS where no treatment is used as reference category, an artificially increased risk for recent use might become apparent as has been shown in this analysis of RCT data, even when there is no true difference in a proper comparison of like with like. The descriptive findings of this final CSR together with the evidence generated in the analyses of RCT data suggest that the HR estimates for all-cause mortality comparing recent and past use with never use as implemented in this PASS should be interpreted with great caution as they possibly result from the informative transition of roflumilast treated patients from current to recent use status at the time of discontinuation.

In GER, an increased risk was observed for recent and past use of roflumilast in the cumulative exposure duration categories of 12 to 24 months and >24 months. In SWE, an increased risk was observed for past use in each cumulative exposure category and for recent use when cumulative exposure was >24 months (Table 43). Although adjusted HRs are numerically elevated the apparent increase in mortality risk should be interpreted accounting for the combination of two distinct factors that may artificially move the estimates away from the null: 1) the confounding effect introduced with the informative discontinuation event of exposed patients, as discussed in the paragraph above; and 2) the increasing imbalance of markers of COPD severity and overall morbidity over time that has been shown in all countries in this report.

Current roflumilast exposure was considered as the main exposure modality in the secondary outcome analyses (except for cancer). The findings of this report are in line with those of the third interim report indicating that the increased risk observed for current roflumilast use with respect to respiratory disease related hospitalisations appears to be driven by a higher risk of hospitalisations for COPD exacerbations. Descriptive analyses of the distribution of different types of respiratory disease related hospitalisations confirmed that COPD exacerbations are by far the most frequent cause of hospitalisation in all countries, accounting for the majority of the hospitalisations for respiratory diseases in GER and SWE and, for approximately 50% of those in the US. While 81.4% ,78.8%, and 54.3% of exposed patients in GER, SWE, and the US, respectively, had a hospitalisation for COPD exacerbation, this was only the case in 74.3%, 70.0%, and 46.5% of unexposed patients in GER, SWE, and the US, respectively (Table 25). This is in apparent contrast with evidence from RCTs (Martinez 2015, Martinez 2016) which showed that roflumilast reduced COPD exacerbation rates and it is also contrary to recommendations based on these trials that roflumilast should be used to reduce COPD exacerbations in patients with severe COPD (Wedzicha 2017). The observed higher respiratory disease hospitalisation rates rather substantiate the interpretation of residual confounding by COPD severity, with the roflumilast treated population experiencing higher frequency of hospitalisation for COPD than the unexposed due to a more severe COPD.

The increased risk of all-cause hospitalisations for current roflumilast use is assumed to be related to the higher risk of respiratory disease related hospitalisations, since a large proportion of all hospitalisations were due to hospitalisations for respiratory diseases. In all countries, the risk estimates were lower for all-cause hospitalisations than for respiratory disease related hospitalisations likely due to dilution of the risk estimates by the other hospitalisation outcomes.

An increased risk for other secondary outcomes, including new diagnosis of depression, that was noted in the previous reports, was also confirmed in these analyses. Warnings regarding the possibility of more frequent occurrences of suicide and depression in roflumilast users have already been implemented into the SmPC based on findings from clinical trials (Daxas SmPC 2011). Several studies have shown an association between depression and suicidal ideation and COPD, which is stronger in more severe COPD (Hegerl and Mergl 2014, Strid 2014). Roflumilast has been studied as an add-on treatment for depression (Study NCT04751071). As both risk factors for depression and suicidal ideation and severity of disease cannot comprehensively be assessed in secondary data, it is possible that the results are prone to unmeasured confounding.

Hospitalisation due to diarrhoea of non-infectious origin and abnormal and unexplained weight loss were associated with a statistically significant risk increase during ongoing roflumilast treatment. Since these safety concerns were identified in the clinical development programme they are already described in the roflumilast SmPC.

Higher quality data on cancer (eg, regarding the completeness of cancer ascertainment, the fact that cancer diagnoses are morphologically confirmed, and that incident and prevalent cancers can be distinguished) are available for SWE than for GER and the US where cancer data are based on claims data. Data in SWE indicate no significant increase in cancer risk overall or for solid tumours for roflumilast exposure without latency period. Similar results, although some confidence intervals not covering 1, were observed in GER, the US and SWE across remaining latency periods. A major weakness in the interpretation of cancer data is the lack of robust data on smoking in all 3 countries. Due to the increased COPD exacerbation risk among smokers and the fact that roflumilast is indicated to reduce COPD exacerbations, smoking may be more prevalent and of higher intensity in patients using roflumilast thereby confounding the apparent association between roflumilast and new malignancies in all countries.

11.4 Generalisability

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. The study was therefore designed to quantify any association between roflumilast treatment and risk of death by comparing the risk of death between roflumilast treated and untreated patients. In pharmacoepidemiology, PS matching is a well-established methodology to balance the probability of treatment selection between populations that are compared in the analyses, to attempt to mimic the randomisation in an RCT. This was the method of choice in this study in the attempt to minimise selection and information bias and to control for confounding. Such an approach provided the highest possible internal validity that was necessary to quantify the

association of interest, in line with the main scope of the study. However, as discussed, despite a thorough PS matching procedure, the baseline balance between treated and untreated cohorts was still imperfect, balance of markers of COPD severity and morbidity deteriorated over time and residual confounding is a distinct possibility. Additional adjustment for risk factors including disease severity markers when estimating HRs provided additional confounding control but further residual confounding is likely, considering the lack of, or incomplete data on smoking and other markers of COPD severity. The matching resulted in the exclusion of a very small proportion of roflumilast-exposed patients with higher PS values for whom matching unexposed COPD patients could not be found. Nonetheless, this large multinational study offers evidence generated in real-world practice that in some aspects can ensure a higher degree of generalisability compared to the evidence produced in the experimental context of randomised trials. Furthermore, evidence generated in all countries shows that among the roflumilast-treated unmatched patients only a few had PS values not represented among the roflumilast-treated matched patients, which further supports the generalisability of the study results.

In SWE, nationwide registers were utilised assuring that the results are generalisable to the Swedish COPD population corresponding to the inclusion criteria of this study. As the inclusion criteria for this study were not very restrictive and the patients in the study population were typical for COPD patients, a high external validity is assumed. A total of 15 of 3234 roflumilast-exposed patients (0.5%) with very severe COPD were excluded in SWE since no matches could be found. Exclusion of these patients does not compromise the internal validity of the study. Since the proportion of excluded patients is low, results also largely apply to the very severe COPD population.

In GER, the GePaRD was used, which includes health insurance data from about 25 million individuals overall and from about 17% of the German population cross-sectionally. Analyses regarding the age and sex distribution, the number of hospital admissions and drug use have shown that the database is representative for GER (Schink and Garbe 2010a, Schink and Garbe 2010b, Fassmer and Schink 2014) and that the insurance population is rather stable over time. High external validity to the German population overall is therefore assumed. In GER, 542 of all 9325 (5.8%) roflumilast exposed COPD patients had to be excluded since no matches could be found.

In the US, the MHS database was used, which provides data on all US military personnel, their dependents, and retirees receiving healthcare. This database is known to differ from the civilian population by race/ethnicity and education level which might affect external validity. In the US, 43 of 9598 roflumilast-exposed patients (0.4%) with very severe COPD could not be matched and were excluded from this study. Overall, a fairly representative sample of roflumilast-exposed patients with respect to COPD severity is considered to be evaluated in this study.

Across all countries, excluded unmatched roflumilast-exposed patients had approximately a 2-fold increased mortality relative to matched roflumilast-exposed patients. The distribution of their PS values compared to that of the matched roflumilast-exposed patients, further confirmed the extreme COPD severity among unmatched roflumilast-exposed patients, thus

raising the question whether roflumilast might have been used as last resort in these excluded patients.

12. OTHER INFORMATION (NOT APPLICABLE)

13. CONCLUSION

The results of this final report 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. 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 3 countries that is likely due to confounding by indication, informative censoring/selection bias over time, and important missing variables such as FEV_1 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).

At a request from the EMA, a meta-analysis was conducted for 5-year all-cause mortality. Results showed substantial between-country heterogeneity with increased mortality risks in two countries (GER and the US) and largely no elevated risks, and even some protective effects, in SWE. Since this heterogeneity cannot be solved by statistical methods (eg, by random effects models), it was decided to only present the country-specific results in the Abstract and not the results of the meta-analysis (which are presented in the Study Report for completeness). In contrast to GER and the US, where data availability before CED was

limited to 1-2 years, there was long data availability before CED in SWE which made it possible to include the variable “duration of COPD” into the PS model. Since “duration of COPD” is an important marker of COPD severity, inclusion of this variable into the PS model presumably achieved better balance between the exposed and unexposed cohort with respect to COPD severity, possibly explaining the discrepancies in the results between SWE and GER/US.

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15. TABLES NOT INCLUDED IN THE TEXT

Table 50 Sensitivity Analysis of 5-year All-cause Mortality According to Ever-Versus-Never Use of Roflumilast Excluding Patients Who Died Within the First 3 and 12 Months After Cohort Entry in Germany

All-cause mortality	GER	
	Never (ref)	Ever
Excluding patients who died within the first 3 months		
Deaths (person-years)	10593 (147010)	3012 (32214)
N at risk	39440	8514
Crude HR (95% CI)	1	1.11 (1.07, 1.16)
Adjusted HR[a] (95% CI)	1	1.06 (1.02, 1.10)
Excluding patients who died within the first 12 months		
Deaths (person-years)	7721 (111881)	2481 (25863)
N at risk	34249	7903
Crude HR (95% CI)	1	0.97 (0.93, 1.02)
Adjusted[a] HR (95% CI)	1	0.91 (0.87, 0.96)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). This model assumes different baseline hazards for each stratum. Strata were defined as PS quintiles per cohort entry year. Analysis stratified by excluding patients who died within the first 3 months and patients who died within the first 12 months of exposure.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; PS = propensity score; ref=reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11b, Table 11c, Table 35b, Table 35c, Table 37b, Table 37c

Table 51 Sensitivity Analysis of 5-year All-cause Mortality According to Ever-Versus-Never Use of Roflumilast Excluding Patients Who Died Within the First 3 and 12 Months After Cohort Entry in SWE

All-cause mortality	SWE	
	Never (ref)	Ever
Excluding patients who died within the first 3 months		
Deaths (person-years)	5309 (52247)	1373 (11349)
N at risk	14696	3130
Crude HR (95% CI)	1	1.15 (1.08, 1.22)
Adjusted HR[a] (95% CI)	1	1.00 (0.94, 1.07)
Excluding patients who died within the first 12 months		
Deaths (person-years)	3,701 (39,141)	1,130 (9,055)
N at risk	12,271	2,881
Crude HR (95% CI)	1	1.27 (1.19, 1.36)
Adjusted[a] HR (95% CI)	1	1.08 (1.00, 1.16)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). This model assumes different baseline hazards for each stratum. Strata were defined as PS quintiles per cohort entry year. Analysis stratified by excluding patients who died within the first 3 months and patients who died within the first 12 months of exposure.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; N = number of patients; PS = propensity score; ref=reference; SWE = Sweden

Sources: Appendix 2.1 Table 58

Table 52 Sensitivity Analysis of 5-year All-cause Mortality According to Ever-Versus-Never Use of Roflumilast Excluding Patients Who Died Within the First 3 and 12 Months After Cohort Entry in the US

	US	
All-cause mortality	**Never (ref)**	**Ever**
Excluding patients who died within the first 3 months		
Deaths (person-years)	15306 (155774)	4269 (32441)
N at risk	44018	9275
Crude HR (95% CI)	1	1.29 (1.25, 1.34)
Adjusted HR[a] (95% CI)	1	1.19 (1.15, 1.24)
Excluding patients who died within the first 12 months		
Deaths (person-years)	10541 (113789)	3396 (25,744)
N at risk	35863	8354
Crude HR (95% CI)	1	1.36 (1.31, 1.42)
Adjusted[a] HR (95% CI)	1	1.24 (1.19, 1.29)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). This model assumes different baseline hazards for each stratum. Strata were defined as PS quintiles per cohort entry year. Analysis stratified by excluding patients who died within the first 3 months and patients who died within the first 12 months of exposure.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; N = number of patients; PS = propensity score; ref=reference; US = United States

Sources: Appendix 3.1 Table 58

Table 53 Sensitivity Analyses for 5-Year All-cause Mortality for Current Use Versus Never Use of Roflumilast Applying a Gap Extension of 100% and No Gap Extension

All-cause mortality	With 100% roflumilast gap extension				Without roflumilast gap extension		
	Never (ref.)	Current	Recent	Past	Current	Recent	Past
GER[a]							
Deaths (person-years)	12071 (160716)	1358 (16062)	159 (1226)	1713 (17165)	1051 (13803)	291 (2084)	1888 (18567)
N at risk	41,718	8775	6646	6011	8775	8236	6805
Crude HR (95% CI)	1	0.97 (0.92, 1.03)	1.61 (1.37, 1.88)	1.36 (1.29, 1.43)	0.87 (0.81, 0.92)	1.67 (1.48, 1.88)	1.38 (1.31, 1.44)
Adjusted[b] HR (95% CI)	1	0.97 (0.91, 1.02)	1.50 (1.28, 1.76)	1.25 (1.19, 1.32)	0.87 (0.81, 0.93)	1.58 (1.41, 1.78)	1.27 (1.21, 1.34)
SWE							
Deaths (person-years)	6104 (57594)	435 (4678)	98 (626)	942 (6835)	542 (5362)	56 (431)	877 (6346)
N at risk	15776	3234	2925	2416	3234	2373	2230
Crude HR (95% CI)	1	0.86 (0.79, 0.94)	1.14 (0.88, 1.49)	1.35 (1.26, 1.45)	0.79 (0.72, 0.87)	1.28 (1.05, 1.57)	1.34 (1.25, 1.44)
Adjusted[b] HR (95% CI)	1	0.81 (0.74, 0.88)	0.99 (0.76, 1.30)	1.12 (1.04, 1.21)	0.75 (0.68, 0.83)	1.13 (0.92, 1.38)	1.12 (1.04, 1.20)
US							
Deaths (person-years)	17539 (171688)	1693 (15463)	444 (2001)	2453 (17316)	2123 (17342)	230 (1316)	2237 (16122)
N at risk	47,151	9598	8627	6998	9598	7078	6307
Crude HR (95% CI)	1	1.11 (1.06, 1.16)	1.61 (1.41, 1.84)	1.39 (1.33, 1.46)	0.99 (0.94, 1.04)	2.00 (1.82, 2.20)	1.41 (1.36, 1.48)
Adjusted[b] HR (95% CI)	1	1.04 (0.99, 1.09)	1.50 (1.32, 1.71)	1.28 (1.22, 1.33)	0.93 (0.88, 0.98)	1.90 (1.73, 2.09)	1.30 (1.24, 1.35)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). This model assumes different baseline hazards for each stratum. Strata were defined as PS quintiles per cohort entry year. Analysis stratified by 100% gap extension and no cap extension.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; PS = propensity score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11a2, Table 11a3; Appendix 2.1 Table 41; Appendix 3.1 Table 43

Table 54 5-Year All-cause Mortality Associated with Number of Roflumilast Dispensations Versus Never Use in GER, SWE, and the US

All-cause mortality	Number of dispensations				
	Never (ref.)	1	2-3	4-9	≥10
GER[a]					
Deaths (person-years)	12071 (160716)	1129 (12782)	697 (7097)	769 (7856)	635 (6718)
N at risk	41718	8775	5925	4325	2816
Crude HR (95% CI)	1	1.16 (1.09, 1.23)	1.22 (1.13, 1.32)	1.23 (1.14, 1.32)	1.09 (1.01, 1.19)
Adjusted[b] HR (95% CI)	1	1.08 (1.01, 1.14)	1.15 (1.07, 1.24)	1.19 (1.10, 1.28)	1.11 (1.02, 1.20)
SWE					
Deaths (person-years)	6104 (57594)	583 (3514)	341 (2526)	297 (1792)	254 (4306)
N at risk	15776	1059	707	522	946
Crude HR (95% CI)	1	1.60 (1.47, 1.74)	1.21 (1.09, 1.35)	1.46 (1.30, 1.64)	0.53 (0.47, 0.60)
Adjusted[b] HR (95% CI)	1	1.20 (1.10, 1.31)	1.11 (0.99, 1.24)	1.29 (1.15, 1.46)	0.52 (0.46, 0.59)
US					
Deaths (person-years)	17539 (171688)	1372 (8103)	841 (5078)	1073 (5346)	1304 (16252)
N at risk	47,151	2537	1564	1742	3755
Crude HR (95% CI)	1	1.71 (1.62, 1.81)	1.57 (1.47, 1.69)	1.86 (1.75, 1.98)	0.74 (0.70, 0.78)
Adjusted[b] HR (95% CI)	1	1.52 (1.43, 1.60)	1.43 (1.33, 1.53)	1.64 (1.54, 1.74)	0.72 (0.68, 0.77)

[a] Compared to Table 11, the number of matched patients is lower as some patients had to be excluded post-hoc due to an update of the database.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). This model assumes different baseline hazards for each stratum. Strata were defined as PS quintiles per cohort entry year.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; PS = propensity Score; ref. = reference; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11f, Table 35f, Table 37f; Appendix 2.1 Table 45; Appendix 3.1 Table 47

Table 55 Crude and Adjusted Hazard Ratios of 5-year All-cause Mortality Associated with Ever Versus Never Roflumilast Use Stratified by FEV_1 Values in GER

FEV_1 status	Number at risk	Number of deaths (PY)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
FEV_1 unspecified				
Never use	7442	1544 (31593)	1 (ref.)	1 (ref.)
Ever use, FEV_1 unspecified	2576	806 (10402)	1.48 (1.35, 1.61)	1.36 (1.24, 1.49)
FEV_1 <35%				
Never use	6104	2544 (19799)	1 (ref.)	1 (ref.)
Ever use, FEV_1 <35%	2684	1251 (9862)	1.01 (0.95, 1.08)	0.96 (0.90, 1.03)
FEV_1 between 35% and <50%				
Never use	2263	698 (8429)	1 (ref.)	1 (ref.)
Ever use, FEV_1 ≥35 % and <50%	1337	460 (5467)	1.00 (0.89, 1.13)	0.99 (0.87, 1.11)
FEV_1 between 50% and <70%				
Never use	445	103 (1833)	1 (ref.)	1 (ref.)
Ever use, FEV_1 ≥50% and <70%	339	102 (1384)	1.31 (0.99, 1.72)	1.30 (0.97, 1.73)
FEV_1 ≥70%				
Never use	15	2 (71)	1 (ref.)	1 (ref.)
Ever use, FEV_1 ≥70%	15	3 (62)	3.00 (0.31, 28.84)	N/A

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; GER = Germany; HR = hazard ratio; PS = propensity score; PY = person-years; ref. = reference

Source: Appendix 1 Table 11e1, Table 11e2, Table 11e3, Table 11e4, Table 11e5, Table 35 e1, Table 35 e256, Table 35 e257, Table 35 e4, Table 35 e5, Table 37 e1, Table 37 e2, Table 37 e3, Table 37 e4, Table 37 e5

Table 56 FEV_1 Values of Patients at Cohort Entry in Matched Roflumilast Exposed and Unexposed Patients by PS Quintiles in GER

	1st quintile		2nd quintile		3rd quintile		4th quintile		5th quintile	
FEV_1 status	**Exposed N=1752**	**Unexposed N=8750**	**Exposed N=1756**	**Unexposed N=8770**	**Exposed N=1758**	**Unexposed N=8784**	**Exposed N=1755**	**Unexposed N=8722**	**Exposed N=1754**	**Unexposed N=6692**
FEV_1 <35%	147 (8.39)	870 (9.94)	325 (18.51)	1588 (18.11)	570 (32.42)	2759 (31.41)	876 (49.91)	4055 (46.49)	1205 (68.70)	4103 (61.31)
FEV_1 ≥35% and <50%	152 (8.68)	627 (7.17)	302 (17.20)	1610 (18.36)	493 (28.04)	2518 (28.67)	484 (27.58)	2766 (31.71)	405 (23.09)	1781 (26.61)
FEV_1 ≥50% and <70%	175 (9.99)	828 (9.46)	257 (14.64)	1309 (14.93)	195 (11.09)	1013 (11.53)	105 (5.98)	605 (6.94)	44 (2.51)	325 (4.86)
FEV_1 ≥70%	46 (2.63)	297 (3.39)	43 (2.45)	229 (2.61)	26 (1.48)	93 (1.06)	19 (1.08)	49 (0.56)	8 (0.46)	43 (0.64)
Not assessable or unspecific	1232 (70.32%)	6128 (70.03%)	829 (47.21%)	4034 (46.00%)	474 (26.96%)	2401 (27.33%)	271 (15.44%)	1247 (14.30%)	92 (5.25%)	440 (6.58%)

FEV_1 = forced expiratory volume in 1 second; GER = Germany; N = number of patients; PS = propensity score
Source: Appendix 1 Table 4h

Table 57 5-year All-cause Mortality According to Ever-Versus-Never Use of Roflumilast for Patients with and Without Asthma

All-cause mortality	GER		SWE		US	
	With asthma	Without asthma	With asthma	Without asthma	With asthma	Without asthma
Deaths (person-years)	1162 (14331)	1859 (18043)	271 (2126)	1104 (9223)	2231 (18369)	2149 (14793)
N at risk	3536	4704	576	2442	4969	4191
Crude HR (95% CI)	1.34 (1.25, 1.44)	1.12 (1.06, 1.18)	1.30 (1.11, 1.53)	1.03 (0.96, 1.10)	1.27 (1.21, 1.34)	1.25 (1.19, 1.32)
Adjusted [a] HR (95% CI)	1.20 (1.11, 1.29)	1.11 (1.05, 1.17)	0.96 (0.80, 1.15)	0.95 (0.89, 1.02)	1.12 (1.06, 1.18)	1.22 (1.15, 1.29)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 14) + markers of COPD severity and morbidity (Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country. Strata without one exposed and without one control were removed from the analysis. Analysis stratified by exposure to asthma.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; GER = Germany; HR = hazard ratio; N = number of patients; PS = propensity score; SWE = Sweden; US = United States

Sources: Appendix 1 Table 11d1, Table 11d2, Table 35 d2, Table 37 d2.1; Appendix 2.1 Table 46; Appendix 3.1 Table 48

APPENDICES