PASS Study Report	
Active substance	R03DX07 Roflumilast
Product reference	EMEA/H/C/001179; PASS study code ID: D7120R00003
Version number	1
Date	12 April 2023

Long-term Post-marketing Observational Study of the Safety of DAXAS™ (roflumilast) – Results of Data from Norway - Addendum Report

Marketing Authorisation Holder(s)

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

Principal Investigator Date

PASS INFORMATION

Title	Long-term post-marketing observational study of the safety of roflumilast
Version identifier of the Final Study Report	Version 1.0
Date of the Final Study Report	14 December 2022
Date of Addendum to Final Study Report	18 April 2023
EU PAS register number	EUPAS14852
Active substance	R03DX07 *Roflumilast*
Medicinal product	*Daxas™*
Product reference	Daxas™ EMEA/H/C/001179 PASS study code ID: D7120R00003
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

Background

This observational cohort study was conducted using databases in Germany (GER), Sweden (SWE), the United States (US), and Norway (NOR). NOR was added to this study based on the EMA PRAC response to the revised first interim report for this PASS, submitted on 05 March 2018. The EMA requested that AstraZeneca conduct additional analysis including the addition of data from another Nordic country. Analyses for GER, SWE, and the US separately and combined are presented in the Final CSR. However, results from NOR were not available at the time of the Final CSR and are therefore reported separately in this addendum. For further details on the study design and results, see the Final CSR.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. ABSTRACT

Title

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

Keywords

See the Abstract of the Final Clinical Study Report (CSR).

Rationale and background

See the Abstract of the Final CSR.

Research question and objectives

See the Abstract of the Final CSR.

Study design

An observational cohort study was conducted using databases in Germany (GER), Sweden (SWE), the United States (US), and Norway (NOR). Analyses were conducted and were presented for GER, SWE, and the US separately and combined in the Final CSR. However, results from NOR were not available at the time of the Final CSR and are reported separately in this addendum. For further details on the study design, see the Abstract of the Final CSR.

Setting

The data reported in this addendum were obtained from electronic national healthcare databases in 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 chronic obstructive pulmonary disease (COPD) patients who had or had not been exposed to roflumilast. In the NOR data, the study population consisted of 9472 individuals (1624 exposed to roflumilast).

Variables and data sources

See the Abstract of the Final CSR.

Statistical Methods

See the Abstract of the Final CSR.

Results

The results presented here, and in the rest of this addendum to the Final CSR are for NOR, as all results for the other countries included in this study have been presented in the Final Study Report dated 14 December 2022.

Matching on propensity score (PS): Like in the other countries, over 95% of roflumilast-exposed patients were matched to at least one unexposed patient in NOR. Overall, 18 out of

1642 roflumilast-exposed patients were excluded since no match with similar age, sex, cohort entry year, and PS could be found. The majority of the excluded roflumilast-exposed unmatched patients had high PS, indicating more severe COPD and therefore a higher risk of the endpoints of interest. However, the matched cohort also included patients with PS scores almost as high as the most severe roflumilast-exposed unmatched patients. Roflumilast-exposed patients without matches were younger, more commonly female, and had higher COPD severity than roflumilast-exposed 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 before cohort entry date (CED), COPD exacerbations, and treatment intensity score (TIS).

After matching, the PS distribution at cohort entry (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 current use of acetylcysteine, number of emergency room visits due to COPD in the 30 days before CED, number of outpatient physician office visits for COPD in the month prior to CED, use of systemic corticosteroids, and number of hospitalisations for any cause. 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, 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 approximately 50% of exposed patients. On the other hand, the proportion of exposed patients with > 10 dispensations ranged from 29.4% in 2012 to 32.9% in 2011.

Duration of follow-up: The median follow-up time was approximately 5.0 years across cohorts: 1844 (Q1-Q3: 716-2264) days for never-exposed patients and 1848 (Q1-Q3: 868-2276) days for ever-exposed patients in NOR

Primary outcome: There was no statistically significant association between exposure to roflumilast and mortality for ever-versus-never exposure to roflumilast, with an adjusted HR of 1.00 (95% CI: 0.92, 1.08).

Analyses by exposure status defined as current, recent, and past indicated a reduced risk of mortality during current use as the adjusted HR was 0.77 (95% CI: 0.67, 0.87). An elevated risk was observed during recent use (HR: 1.42, 95% CI 1.04, 1.93) and past use (HR: 1.15, 95% CI: 1.04, 1.27).

In analyses by cumulative exposure categories, there was no statistically significant increase in mortality with increasing exposure durations compared to never use. The adjusted HRs (95% CI) were 0.92 (0.79, 1.07) for 0 to 3 months cumulative exposure, 1.10 (0.98, 1.23) for

3 to 12 months cumulative exposure, 0.97 (0.79, 1.20) for 12 to 24 months of cumulative exposure, and 0.87 (0.72, 1.05) for > 24 months cumulative exposure.

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 were below 1 (ie, indicating a reduced mortality for roflumilast). Results were statistically significant for all cumulative exposure categories, except the 12 to 24 months cumulative exposure category.
- Analyses stratified by the number of roflumilast dispensations throughout follow-up did not demonstrate a consistent increase in mortality with increasing roflumilast exposure. There was a significant increase in mortality for all dispensation categories, except for ≥ 10 dispensations of roflumilast compared to never use.
- In the high-dimension propensity score (HDPS)-matched patients, the mortality was similar in the roflumilast-exposed cohort compared to the unexposed cohort (adjusted HR: 0.99 [0.91, 1.08]) and similar to the results from the analysis using conventional PS matching.

Secondary outcomes: There was an increased risk of respiratory disease-related hospitalisation, hospitalisation for any cause, and hospitalisation for diarrhoea comparing current use of roflumilast with never use. Significant increases were seen for past use for hospitalisations due to pulmonary embolism and for recent use for new diagnoses of tuberculosis or hepatitis B or C or other severe viral hepatitis (except hepatitis A); these increases were offset by a wide CI and may be due to the small number of patients with these events. No statistically significant increase of the risk of any malignancy was observed. The adjusted HRs for new diagnosis of solid tumour with no latency, in ever-versus-never exposure to roflumilast was 0.94 (95% CI: 0.80, 1.09). Estimates did not change substantially with 1 or 2 years of latency.

Meta-analysis: There was considerable between-country heterogeneity (I^2 = 90%) in the meta-analysis of the results of roflumilast use (ever versus never) and association with 5-year all-cause mortality. Results from GER and the US showed a slightly increased 5-year mortality for ever versus never use, while there were no indications of increased mortality in SWE and NOR. Due to the presence of this degree of heterogeneity which hampers interpretation of outputs from the meta-analysis, the results of meta-analysis are only presented for completeness.

Conclusion

The results for the primary outcome in the main analysis for NOR were consistent with the results for SWE. In the comparison of ever use of roflumilast versus never use, no increased risk in mortality was observed in SWE and NOR while some increase in risk was seen in GER and the US as presented in the Final Study Report. In the sensitivity analysis for the primary

outcome where exposure was explored using exposure status at event (current, recent, and past), the NOR results were similar to SWE, GER, and the US where no increased risk was observed in current roflumilast users and a less than 1.5-fold increase in risk was observed for the recent and past use categories. In further sensitivity analysis, investigating cumulative exposure time (0 to 3 months, 3 to 12 months, 12 to 24 months, and > 24 months) results in NOR were similar to SWE, with no increase in mortality observed (as opposed to in GER and the US, where increased risks were generally observed). Finally, in the sensitivity analysis censoring patients at first discontinuation, results in NOR were similar to those in SWE and the US with no increase in risk observed.

Consistent with what was observed in GER, SWE, and the US, descriptive and analytical findings in NOR 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. The results of the HDPS for NOR were similar to the results from the analyses using conventional PS matching; hence this methodology may have been insufficient to completely eliminate the presence of residual and unmeasured confounders.

As was observed with GER, US, and SWE, a statistically significant increased risk was observed for respiratory disease-related hospitalisations, and all-cause hospitalisation that is likely due to confounding by indication, informative censoring/selection bias over time, and important missing variables such as forced expiratory volume in 1 second and smoking. There was also a statistically significant increased risk observed for hospitalisation due to diarrhoea, a known side effect of roflumilast. However, no new risks compared with those that already emerged in the clinical development programme were observed. The risk of cancer was not significantly elevated for any latency category in NOR; this agrees with the outcome in SWE. In NOR as well as SWE, data were derived from a cancer registry with better data quality (in comparison to GER and the US which are based on claims data).

A meta-analysis was conducted for 5-year all-cause mortality for all 4 countries where the study was conducted. Results of the meta-analysis of all 4 countries showed substantial between-country heterogeneity with generally increased risks in 2 countries (GER and the US), and largely no elevated risks in SWE and NOR. In contrast to GER and the US, in NOR and SWE the variable “duration of COPD” was included in the PS model. Since “duration of COPD” is an important marker of COPD severity, inclusion of this variable into the PS model presumably gave a better balance between the exposed and unexposed cohort with respect to COPD severity, which might explain the discrepancies in the results between NOR and SWE compared to GER and US.

Marketing Authorisation Holder(s)

AstraZeneca AB, Sweden

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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
CE	cohort entry
CED	cohort entry date
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSR	clinical study report
DDD	defined daily dose
EMA	European Medicines Agency
EU	European Union
GER	Germany
GPI	generic product identifier
HDPS	high-dimension propensity score
HR	hazard ratio
ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
ICS	inhaled corticosteroid
IR	incidence rate
ITT	intent-to-treat
LABA	long-acting β_2-agonist
MR	mortality rate
MRR	mortality rate ratio
NOR	Norway
PASS	post-authorisation safety study
PS	propensity score
PY	person-years
Q1	first quartile
Q3	third quartile
RCT	randomised controlled trial
SABA	short-acting β_2-agonist
SAP	statistical analysis plan
SD	standard deviation
SWE	Sweden
TIS	treatment intensity score
US	United States

3. INVESTIGATORS

The investigators are provided in Section 3 of the Final CSR.

4. OTHER RESPONSIBLE PARTIES

The members of the Independent Scientific Advisory Committee and responsible parties involved in the conduct of the study are provided in Section 4 of the Final CSR.

5. MILESTONES

The milestones that were planned and/or met are provided in Section 5 of the Final CSR. In addition, the following milestone is related to the current CSR Addendum:

Milestone	Planned date	Actual date	Comments
Addendum - Results for Norway	May 2023	May 2023	Results have been separately reported for Norway because they were not available at the time of the final CSR

6. RATIONALE AND BACKGROUND

The rational and background for this study is provided in Section 6 of the Final CSR. This addendum to the Final CSR presents the results of data from NOR for 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.

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), Norway in October 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.

7. RESEARCH QUESTION AND OBJECTIVES

The primary, secondary, and exploratory objectives are provided in Section 7 of the Final CSR.

8. PROTOCOL AMENDMENTS AND UPDATES

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

9. RESEARCH METHODS

9.1 Study Design

This addendum report describes the results for Norway in a multi-country, non-interventional PASS using patient-level secondary data from different databases. The study was based on patient-level data from different electronic healthcare databases from 4 countries deemed relevant based on reimbursement status and number of roflumilast-treated patients: GER, SWE, the US, and NOR (as detailed in Section 9.5 of Final CSR). Analyses were conducted and were presented for GER, SWE, and the US separately and combined in the Final CSR. However, results from NOR were not available at the time of the Final CSR and are reported separately in this addendum.

The study design is described in Section 9.1 of the Final CSR.

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.

9.2 Setting

The setting is described in Section 9.2 of the Final CSR.

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.

Definitions for COPD/chronic bronchitis patients shown in Table 1 are or Norway.

Table 1 Definitions for COPD/Chronic Bronchitis Patients in Norway Used in This Multicountry Study

Diagnosis codes for COPD/chronic bronchitis	Proxy drugs (For COPD/chronic bronchitis diagnosis)
ICD-10:J44, J41-J42	ATC R03BB01, R03BB04, R03BB05, R03BB06, R03AL02, R03AL03, R03AL04

ATC = anatomical, therapeutic, and chemical; COPD = chronic obstructive pulmonary disease; GPI = generic product identifier; ICD = International Classification of Diseases and Related Health
Source: Core SAP, Section 6.1

Further details on the patients are provided in Section 9.3 of the Final CSR.

9.4 Variables

9.4.1 Outcomes

Outcomes of interest were defined as in Table 2.

Table 2 Outcome Variables With Definitions and Coding

Outcome	Definition and coding for Norway
Primary outcome	
5-year all-cause mortality	• Death during the potential follow-up time.
Secondary outcomes	
Death by suicide or hospitalisation for suicide attempt (intentional self-harm or overdose)	• ICD-10: X60-X84 , X6n, X6N, T39-T43
Hospitalisation for any cause	• First hospitalisation after CED
Major cardiovascular events leading to hospitalisation	• Arrhythmia (conduction disorders and dysrhythmias): ICD-10 codes I44, I45 • Myocardial infarction: ICD-10 codes I21, I22 • Cerebral infarction or stroke not specified as haemorrhage or infarction: ICD-10 codes I63, I64 • Heart failure: ICD-10 codes I50 • Pulmonary embolism: ICD-10 codes I26
Respiratory disease-related hospitalisation, including hospitalisation due to COPD/chronic bronchitis exacerbation	• ICD-10 codes J09-J22, J40-J47
New diagnosis of depression (with or without hospitalisation) [a]	• ICD-10 codes F32.2-F32.3 • GPI code 58x
New diagnosis of malignant neoplasm (except non-melanoma skin cancer) [a]	• ICD-10 codes C00-C97 excluding C44 For stratification by solid and haematopoietic tumours: • Solid: ICD-10 codes C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C80, C97 • Haematopoietic: ICD-10 codes C81-C86, C88, C90-C96
Hospitalisation due to diarrhoea of non-infectious origin	• ICD-10 codes K52.9, K59.1
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
New diagnosis of tuberculosis or of hepatitis B or C or other severe viral hepatitis infection (except hepatitis A)	• ICD-10 codes A15, B16-B19

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; ICD = International Classification of Diseases and Related Health Problems.

Source: NOR SAP; Core SAP Table 1 and Table 5

9.4.2 Exposure

The exposure definitions adopted for this study are provided in Section 9.4.2 of the Final CSR.

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 3 during the 4 months before CED. To determine any changes in treatment intensity, use of medications was also explored in the 4-month time window 9 to 12 months before CED (Table 6) and compared to use in the 4 months immediately before CED.

Table 3 Definition of Use of COPD Drugs With Coding 4 Months Before Cohort Entry Date for Norway

Variable	Description	Categories
SAMA use 4 months before CED	Any dispensation of SAMA (ATC codes R03BB01, R03BB02, 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, R03AL02, 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, 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, R03AK11, R03AL03, R03AL04 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, 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; 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

Source: Core SAP Table 1

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 4.

Table 4 Definition of Use[a] of COPD Drugs 9 to 12 Months Before CED for Norway

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.

Source: Core SAP Table 1

9.4.4 Propensity Score Variables

The variables shown in Table 5 were used in constructing the PS for Norway.

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
Demographics		
Sex		• Male • Female
Age	Age at CED	NA
History of alcoholism / alcohol abuse	History of alcoholism (ICD-10 codes E24.4, F10.x, G31.2, G62.1, G72.1, I42.6, K29.2, K70.0-K70.4, K70.9, K85.2, K86.0, O35.4, P04.3, Q86.0, R78.0, T51.0, T51.9, Z50.2, E52, ATC: N07BB01, N07BB03, N07BB04) prior to CED	• History • No history
Obesity	ICD-10 E66.9, E66.0, E66.1, E66.2	-
Treatment and comorbidity history		
Type of care in the 12 months before CED	Type of care in the 12 months before CED	• None • COPD medication • Secondary care • Hospitalisation
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
Medication used in the 4 months before CED, based on 5 binary variables	Treatment used in the 4 months before CED: SABA SAMA LABA LAMA ICS	Yes/no for each medication
TIS in the 4 months before CED, 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

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
Change in treatment intensity over the year before CED	To look at a possible change of severity, the difference was evaluated between intensity of COPD treatment intensity in the 4 months before CED and in the 4-month interval 9 to 12 months before CED.	• Decrease • No changes • Increase 1 • Increase > 1
Number of hospitalisations for any cause in the 12 months before CED	Number of hospitalisations for any cause in the 12 months before CED.	• None • 1 to 2 • 3 to 6 • 6 or more
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.	• None • 1 to 2 • 3 to 5 • 6 or more
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	• Yes • No
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 CD-10 code J09-J22, J40-J43.	• None • 1 to 2 • 3 to 5 • 6 or more
Number of emergency room visits for COPD in the 12 months before CED	Number of emergency room visits in the 12 months before CED due to COPD exacerbation - based on ICD-10 code J44.	• Yes • No
Number of emergency room visits for COPD in the 30 days before CED	Number of emergency room visits in the 12 months before CED due to COPD exacerbation - based on ICD-10 code J44	• Yes • No

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
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 and/or systemic antibiotics or inhaled use of nebulised budesonide during the last 12 months, not indicating chronic use (ie, not exceeding 8-month supply) in conjunction with a diagnosis of COPD.	• None • 1 to 2 • 3 to 5 • 6 or more
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
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
Asthma before CED	Diagnosis (in- or outpatient) of asthma (ICD-10 code J45) any time before CED.	• No • Yes
Emphysema before CED	Diagnosis (in- or outpatient) of emphysema (ICD-10 code J43) any time before CED	• No • Yes
Current use of theophylline at CED	Current use of theophylline (ATC codes R03DA04, or GPI code 430004000x, 44993003301210, 44991002401225, 44991002400130) at CE. All dispensations overlapping CED or ending in the 14-day period before CED.	• No • Yes
Current use of acetylcysteine at CED	Current use of acetylcysteine (ATC code R05CB01 or GPI codes 43300010002003 and 43300010002005) at CE. All dispensations overlapping CE or ending in the 14-day period before CED.	• No • Yes
Charlson Comorbidity Index (CCI)	CCI based on diagnoses any time before CED and as defined in (Quan 2005).	• 0 to 2 • 3 to 5 • Over 5
Pneumonia and influenza in the 12 months before CED	Diagnosis (in- or outpatient) of pneumonia and influenza (ICD-10 codes J09 - J18) in the 12 months before CED.	• No • Yes

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
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) any time before CED.	• No • Yes
Hip fracture in the 12 months before CED	Diagnosis (in- or outpatient) of hip fracture, (ICD-10 code S72) in the 12 months before CED.	• No • Yes
Inflammatory bowel disease before CED	Diagnosis (in- or outpatient) of inflammatory bowel disease (ICD-10 codes K50 and K51) any time before CED.	• No • Yes
Diverticulitis in the 12 months before CED	Diagnosis (in- or outpatient) of diverticulitis (ICD-10 codes K57) in the 12 months before CED.	• No • Yes
Osteoporosis in the 12 months before CED	Diagnosis (in- or outpatient) of osteoporosis (ICD-10 codes M80 - M82) and/or drug treatment for osteoporosis ATC codes M05BA, M05BB.	• No • Yes
Pneumococcal vaccination before CED	Pneumococcal vaccination (CPT codes: 90669, 90670, 90732, G0009) within 5 years before CED.	• No • Yes
Arterial hypertension before CED	Diagnosis (in- or outpatient) of arterial hypertension (ICD-10 codes I10, I11, I12, I13, and I15) any time before CED	• No • Yes
Hyperlipidaemia before CED	Diagnosis (in- or outpatient) of hyperlipidaemia, (ICD-10 code E78) any time before CED.	• No • Yes
Atrial fibrillation before CED	Diagnosis (in- or outpatient) of AF (ICD-10 codes I48.0, I48.1, I48.2, and I48.9) any time before CED.	• No • Yes
DVT in the 12 months before CED	Diagnosis (in- or outpatient) of DVT (ICD-10 code I80) in the 12 months before CED	• No • Yes
Beta-blockers use 4 months before CED	Dispensation of beta-blockers (ATC codes C07) within 4 months before CED	• No • Yes
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
ACE-inhibitors use 4 months before CED	Dispensation of ACE-inhibitors (ATC codes C09A and C09B) within 4 months before CED	• No • Yes

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
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
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
Diuretic use 4 months before CED	Dispensation of diuretics (ATC codes C03 or GPI code 37x) within 4 months before CED	• No • Yes
Antiarrhythmic drug use 4 months before CED	Dispensation of antiarrhythmic drugs (ATC codes C01B) within 4 months before CED	• No • Yes
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
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
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
Digitalis use 4 months before CED	Dispensation of digitalis (ATC codes C01AA or GPI code 31200010x) within 4 months before CED	• No • Yes
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
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
Mood disorder before CED	Diagnosis (in- or outpatient) of mood disorder related to depression (ICD-10 codes F30-F39) and/or use of antidepressant drugs any time before CED	• No • Yes
Psychosis before CED	Diagnosis (in- or outpatient) of mood disorder related to psychosis (ICD-10 codes F20-F29) and/or use of antipsychotic drugs (ATC codes N05AA-N05AL, and N05AX) any time before CED	• No • Yes

Table 5 Propensity Score Variables for Norway

Variable	Description	Categories
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
Hyperthyroidism in the 12 months before CED	Diagnosis (in- or outpatient) of hyperthyroidism (ICD-10 codes E05) and/or use of anti-thyroid drugs (ATC codes H03BA, H03BB, and H03BC) in the 12 months before CED	• No • Yes
Parkinson's disease before CED	Diagnosis (in- or outpatient) of Parkinson's disease (ICD-10 codes G20) and/or use of antiparkinsonian drugs (ATC codes N04) any time before CED	• No • Yes
Smoking any time before CED[c]	Diagnosis (in- or outpatient) of nicotine dependence, tobacco use NOS (ICD-10 codes Z72.0, F17, Z71.6) any time before CED	• No • Yes
Multiple sclerosis before CED	Diagnosis (in- or outpatient) of multiple sclerosis (ICD-10 codes G35) any time before CED.	• No • Yes
Lupus erythematosus before CED	Diagnosis (in- or outpatient) of lupus erythematosus (ICD-10 codes M32) any time before CED.	• No • Yes
Cirrhosis before CED	Diagnosis (in- or outpatient) of cirrhosis (ICD-10 codes K74.3, K74.4, K74.5, and K74.6) any time before CED.	• No • Yes
Immunosuppressive medication use 4 months before CED	Dispensation of immunosuppressants (ATC codes L04) within 4 months before CED	• No • Yes
Suicidal ideation or action any time before CED	Diagnosis (in- or outpatient) of suicidal ideation or action (ICD-10 codes X71-X83, X84.9, Y21-Y33, X6n, or X6N) any time before CED	• No • Yes

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ATC = anatomical, therapeutic and chemical; CCI = Charlson Comorbidity Index; CE = cohort entry; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; CPT = current procedural terminology; DDD = defined daily dose; DVT = deep vein thrombosis; GPI = generic product identifier; ICD = International Classification of Diseases and Related Health Problems; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; NA = not applicable; NOS = not otherwise specified; OPS = Operation and Procedure Code; PS = propensity score; SABA = short-acting β2-agonist; SAMA = short-acting muscarinic antagonist; TIS = treatment intensity score.

Source: NOR SAP; Core SAP Table 1; Appendix 1 Table 13

9.5 Data Sources and Measurement

Data sources used in the study are provided in Section 9.5 of the Final CSR.

9.6 Bias

Sources of bias are provided in Section 9.6 of the Final CSR.

9.7 Study Size

The study size is described in Section 9.7 of the Final CSR.

9.8 Data Transformation

Data transformation is described in Section 9.8 of the Final CSR.

9.9 Statistical Methods

The planned statistical methods are detailed in the Core SAP. Country-specific differences in the analyses are described in the NOR SAP adaptations. The statistical methods are described briefly in Section 9.9 of the Final CSR.

10. RESULTS

The results are presented for GER, SWE, and the US in Section 10 of the Final CSR. The results from NOR are summarised below.

10.1 Participants

The total number of PS-matched patients per year and per country are shown in Table 6.

In NOR for 2011 to 2013, 1642 patients ever exposed to roflumilast and 249438 unexposed patients met the inclusion criteria. After matching, the study population of the 3 annual cohorts included 9472 patients, with 1624 roflumilast-exposed patients matched with 7830 unexposed patients.

Table 6 Patient Accrual in Norway by Study Year

Year	2011	2012	2013	All
Number of patients in study population (PS-matched cohort)	3226	3271	2975	9472
Number of roflumilast-exposed patients with matches	557	564	503	1624
Number of unexposed patients	2660	2704	2466	7830
Number of roflumilast-exposed patients without matches	9	3	6	18
Number of patients counted twice[a]	0	123	137	260

[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.

PS = propensity score.

Source: Appendix 2 Table 1

In the full study cohort including all CE years, 90.7% of exposed patients were matched with 5 unexposed controls in NOR (Table 7).

Table 7 Distribution of the Number of Matches in Norway

	0		1		2		3		4		5		
All years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**Total**
Norway	18	1.10	18	1.10	32	1.95	38	2.31	46	2.80	1490	90.74	1642

N = number of patients

Sources: Appendix 2 Table 2

In NOR, 260 patients 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 8. After PS matching, age and sex were balanced with only negligible differences between the roflumilast-exposed and unexposed cohorts.

Table 8 Age and Sex Distribution at Cohort Entry in The Ever and Never Exposure Cohorts Before and After PS Matching in Norway

	Before matching		After matching	
Variable	**Ever N (%) n=1642**	**Never N (%) n=249438**	**Ever N (%) n=1624**	**Never N (%) n=7830**
Age at CED				
40-44	12 (0.73)	5,025 (2.01)	11 (0.68)	45 (0.57)
45-49	17 (1.04)	8444 (3.39)	16 (0.99)	78 (1.00)
50-54	59 (3.59)	12962 (5.20)	57 (3.51)	242 (3.09)
55-59	110 (6.70)	21511 (8.62)	108 (6.65)	486 (6.21)
60-64	238 (14.49)	31972 (12.82)	236 (14.53)	1052 (13.44)
65-69	431 (26.25)	44774 (17.95)	427 (26.29)	1998 (25.52)
70-74	297 (18.09)	36708 (14.72)	293 (18.04)	1456 (18.60)
75-79	265 (16.14)	33725 (13.52)	265 (16.32)	1298 (16.58)
80+	213 (12.97)	54317 (21.78)	211 (12.99)	1175 (15.01)
Range (min, max)	(41, 96)	(40, 108)	(41, 96)	(41, 97)
Mean (±SD)	69.79 (8.76)	69.55 (11.52)	69.84 (8.70)	70.38 (8.69)

Table 8 Age and Sex Distribution at Cohort Entry in The Ever and Never Exposure Cohorts Before and After PS Matching in Norway

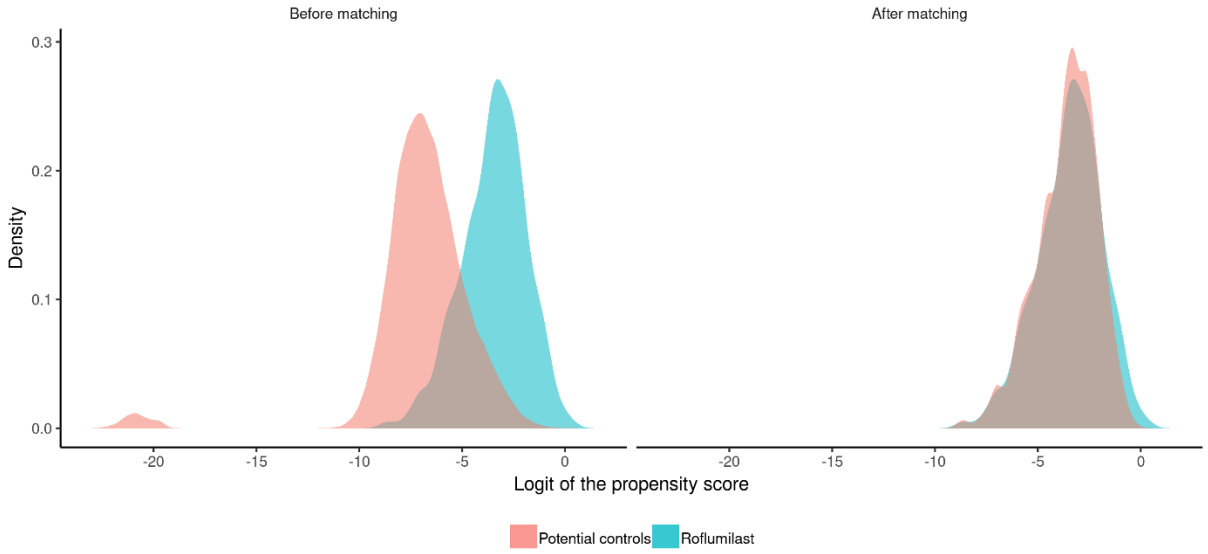
Variable	Before matching		After matching	
	Ever N (%) n=1642	Never N (%) n=249438	Ever N (%) n=1624	Never N (%) n=7830
Median	69	70	69	70
Q1	65	62	65	65
Q3	76	78	76	77
Male	869 (52.92)	123653 (49.57)	861 (53.02)	4128 (52.72)
Female	773 (47.08)	125785 (50.43)	763 (46.98)	3702 (47.28)

CED = cohort entry date; max = maximum; min = minimum; 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.

Source: Appendix 2 Table 3

The outcome of matching based on the PS variables listed in Table 5 is graphically presented in Figure 1 for Norway. 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 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.

Figure 1 PS Distribution of Roflumilast Exposed and Unexposed Patients Before and After Matching Including All Study Years in Norway



PS = propensity score

Source: Appendix 1 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 9 listing variables imbalanced above the predefined threshold of 0.1 standardised difference.

In NOR, 29 of 63 variables were imbalanced before matching and 7 variables remained imbalanced in the all-years cohort after matching (Table 9). Consequently, more roflumilast-exposed unmatched patients (66.7%) had hospitalisations due to COPD exacerbation in the 30 days before CED than roflumilast-exposed matched patients (11.7%) (see Appendix 2, 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.

Table 9 Imbalanced Variables (Standardised Difference >0.1) at CED in Norway

Variable	2011 cohort	2012 cohort	2013 cohort	All years cohort
Current use of acetylcysteine	-	X	X	X
Number of hospitalisations due to COPD in the 12 months before CED	X	X	X	X
Number of hospitalisations due to COPD in the 30 days before CED	X	X	X	X
Number of emergency room visits due to COPD in the 30 days before CED	X	X	-	X
Number of outpatient physician office visits for COPD in the month prior to CED	X	X	X	X
Use of systemic corticosteroids	X	X	-	X
Hip fracture	-	-	X	-
Number of hospitalisations for any cause	X	X	-	X
Number of outpatient physician office visits for COPD in the month prior to CED	X	X	X	X
Number of respiratory disease-related hospitalisations during the last 12 months	-	X	-	-

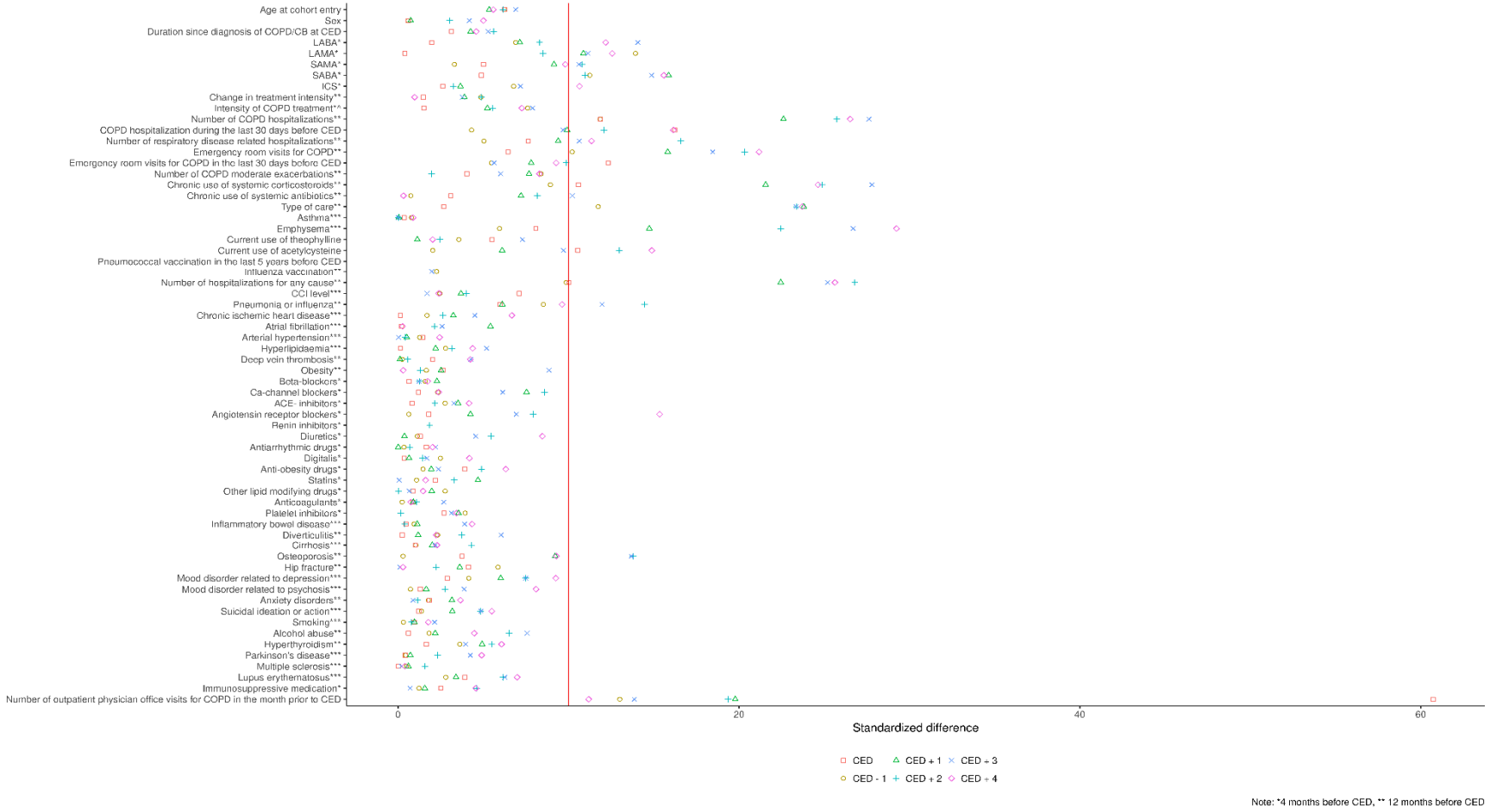
Note: Imbalance defined by a cut-off value of >0.1 in the standardised difference between exposure groups
CED = cohort entry date; COPD = chronic obstructive pulmonary disease.
Source: Appendix 2, Table 4

The balance for all PS variables used in NOR was further examined. Standardised differences observed at -1, 0, 1, 2, 3 and 4 years after matching are displayed in Figure 2.

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. 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 to evaluate the balance for PS variables at CED and at the year prior to baseline (CED-1), despite matching at baseline and achieving a reasonable balance at baseline, further imbalances in variables related to COPD severity were observed at CED-1. These findings suggest 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 2 Standardised Differences for the Propensity Score Variables After Matching at -1, 0, 1, 2, 3 and 4 Years After Matching for Norway



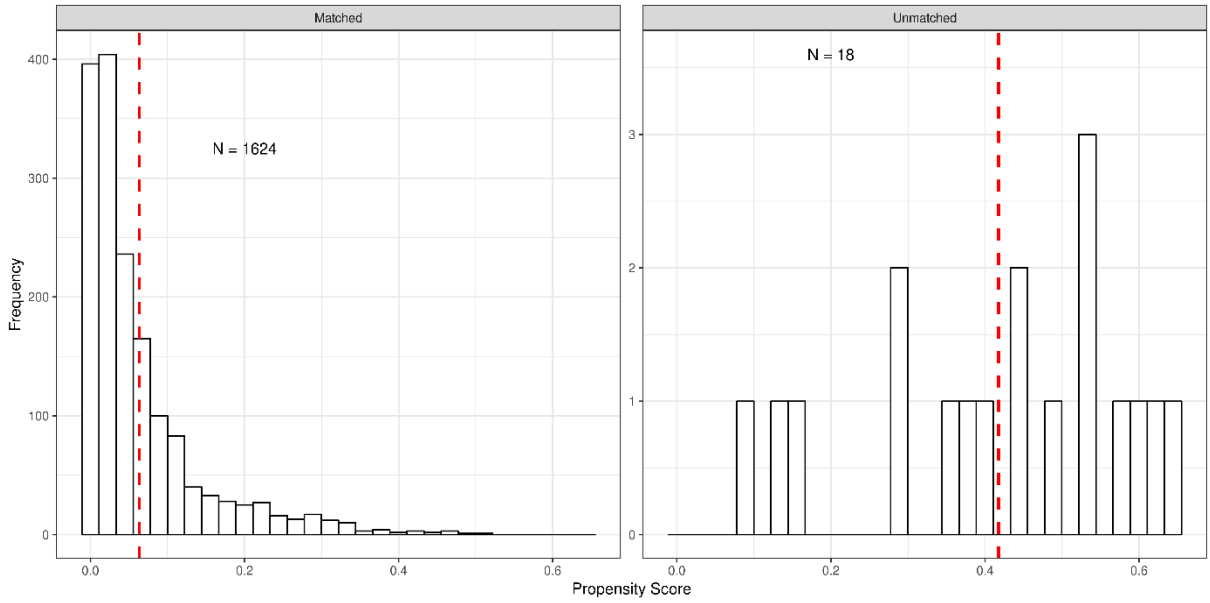
ACE = angiotensin-converting enzyme; CED = cohort entry date; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting beta agonist; SAMA = short-acting muscarinic antagonist

Source: Appendix 2, Figure 1

A total of 18 roflumilast-exposed patients without matches were excluded from the analyses in NOR (Table 10). 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. The distribution of PS of the matched and unmatched patients showed a higher proportion of unmatched patients than matched patients with higher PS (Figure 3). Characteristics of roflumilast-exposed patients with and without matches regarding age, sex and markers of COPD severity are compared in Table 10. Roflumilast-exposed patients without matches were younger and had higher COPD severity than roflumilast-exposed patients with matches, and more commonly female. 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 before CED, COPD exacerbations, and TIS (Table 10).

Figure 3 Standardised Differences for the Propensity Score Variables After Matching at CED-1 and Unmatched Patients Including All Study Years in Norway



Sources: Appendix 3, Figure 1

Table 10 Age, Sex, and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients in Norway

	Exposed with matches	Exposed without matches
	N (%) (n=1624)	N (%) (n=18)
Age		
40-44	11 (0.68)	XXXX
45-49	16 (0.99)	XXXX

Table 10 Age, Sex, and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients in Norway

	Exposed with matches	Exposed without matches
	N (%) (n=1624)	N (%) (n=18)
50-54	57 (3.51)	XXXX
55-59	108 (6.65)	XXXX
60-64	236 (14.53)	XXXX
65-69	427 (26.29)	XXXX
70-74	293 (18.04)	4 (22.22)
75-79	265 (16.32)	0
80+	211 (12.99)	XXXX
Range (min, max)	(41, 96)	(43, 90)
Mean (SD)	69.84 (8.70)	64.95 (12.15)
Median (Q1, Q3)	69 (65, 76)	66 (56, 73)
Sex		
Male	861 (53.02)	8 (44.44)
Female	763 (46.98)	10 (55.56)
Number of hospitalisations due to COPD exacerbations in the 12 months prior to CED		
0 1-2 3-5 6+	1022 (62.93) 430 (26.48) 125 (7.70) 47 (2.89)	XXXX XXXX 7 (38.89) 0
Hospitalisation due to COPD exacerbation in the 30 days before CED	190 (11.70)	12 (66.67)
Number of respiratory disease-related hospitalisations during the past 12 months		
0 1-2 ≥ 3	1235 (76.05) 316 (19.46) 73 (4.50)	8 (44.44) XXXX XXXX
Patients with at least 1 emergency room visit for COPD in the year before CED	575 (35.41)	XXXX
Patients with at least 1 emergency room visit for COPD in the 30 days before CED	217 (13.36)	13 (72.22)
Current use of theophylline at CED	178 (10.96)	6 (33.33)
Current use of acetylcysteine at CED	467 (28.76)	11 (61.11)
Charlson Comorbidity Index		
0-2 3-5 ≥ 6	1178 (72.54) 384 (23.65) 62 (3.82)	XXXX XXXX XXXX
Emphysema	281 (17.30)	7 (38.89)
Number of moderate COPD exacerbations[a]		
0 1-2 3-5 6+	198 (12.19) 363 (22.35) 511 (31.47) 552 (33.99)	XXXX XXXX XXXX 12 (66.67)

Table 10 Age, Sex, and Markers of COPD Severity at Cohort Entry for Matched and Unmatched Roflumilast-exposed Patients in Norway

	Exposed with matches	Exposed without matches
	N (%) (n=1624)	N (%) (n=18)
Treatment intensity score[b]		
0 1-2 3 4	55 (3.39) 280 (17.24) 444 (27.34) 845 (52.03)	0 XXXX XXXX 14 (77.78)
Chronic use of systemic corticosteroids	473 (29.13)	18 (100)
Propensity Score class counts		
1	NR	NR
2	NR	NR
3	NR	NR
4	NR	NR
5	NR	NR

[a] 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 CED).

[b] 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).

Note: XXXX: Counts below 3 not shown to comply with the small cells rule to prevent identification of small counts.

CED = cohort entry date; COPD = chronic obstructive pulmonary disease; 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; NR = not reported; Q1 = first quartile; Q3 = third quartile; SABA = short-acting β_2 agonist; SAMA = short-acting muscarinic antagonist; SD = standard deviation.

Sources: Appendix 2 Table 5

The crude MR in the roflumilast exposed matched and unmatched patients was similar but due to the small number of events for the unmatched cohort, CIs were wide and should be interpreted with caution (Table 11).

Table 11 Mortality Rates Per 1000 Person-years and Mortality Rate Ratio with 95% CIs in Matched and Unmatched Roflumilast-exposed Patients in Norway

	Matched	Unmatched
Deaths (PY)	942 (7126)	11 (78)
N at risk	1624	18
MR (95% CI)	132.19 (124.02, 140.91)	141.33 (78.27, 255.20)
Crude MRR (95% CI)	1.00 (Reference)	1.07 (0.59, 1.94)

CI = confidence interval; MR = mortality rates; MRR = mortality rate ratio; PY = person-years.

Sources: Appendix 2 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 (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 are described in Table 12. Approximately half the patients had 1 to 3 dispensations, and almost one third of patients had 10 or more dispensations in each annual cohort.

The proportion of patients with only 1 roflumilast dispensation was 31.1%, 34.4%, and 35.8% in the 2011, 2012, and 2013 cohorts, respectively.

Table 12 Roflumilast Dispensations by Calendar Year of Cohort Entry Including All Follow-up Time for the Respective Cohort in Norway

Parameter	2011	2012	2013
Number of roflumilast-exposed patients			
Total	557	564	503
Number of roflumilast dispensations per patient			
1-3	288 (51.71)	314 (55.67)	285 (56.66)
1	173 (31.06)	194 (34.40)	180 (35.79)
2	78 (14.00)	81 (14.36)	70 (13.92)
3	37 (6.64)	39 (6.91)	35 (6.96)
4-6	60 (10.77)	56 (9.93)	45 (8.95)
7-9	26 (4.67)	28 (4.96)	19 (3.78)
10-14	31 (5.57)	20 (3.55)	31 (6.16)
15+	152 (27.29)	146 (25.89)	123 (24.45)
Range (min, max)	(1, 156)	(1, 140)	(1, 142)
Mean (±SD)	12.10 (20.20)	10.53 (16.41)	11.08 (20.52)
Median (Q1, Q3)	3 (1, 16)	3 (1, 15)	3 (1, 14)
Distribution of number of DDs dispensed per dispensation			
Range (min, max)	(1, 270)	(1, 360)	(1, 360)
Mean (±SD)	55.61 (37.22)	58.77 (36.65)	53.07 (37.09)
Median (Q1, Q3)	60 (14, 90)	90 (14, 90)	30 (14, 90)

[a] One outlier excluded

DD = daily dose; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

Sources: Appendix 2 Table 7

10.2.2 Descriptive Analyses Related to Follow-up

The follow-up time was comparable in the roflumilast-exposed and unexposed patients (Table 13).

Table 13 Follow-up Time (Days) in Never and Ever Exposed to Roflumilast and the Total Population in Norway

Statistic (days)	Never exposed	Ever Exposed
Range (min, max)	(1, 2918)	(2, 2917)
Mean (±SD)	1552.50 (877.99)	1602.68 (842.23)
Median	1844	1848
Q1	716	868
Q3	2264	2276

max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Sources: Appendix 2 Table 8

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 7830 unexposed patients, 260 (3.32%) 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 PY of follow-up for the roflumilast-exposed and unexposed cohorts are shown in Table 14.

Table 14 5-year All-cause Mortality in Ever-Versus-Never Use of Roflumilast in Norway

5-year all-cause mortality	Ever use (exposed) N of events (PY)	Never use (unexposed) N of events (PY)
Norway	779 (6036)	3251 (28036)

N = number; PY = person-years.
Sources: Appendix 2 Table 9

Table 15 lists the most frequent causes of death in NOR by use status of roflumilast at the time of death (current, recent, past) and never use. The most frequent cause of death in NOR was COPD, accounting for 49.8% of deaths in the unexposed cohort and 59.7% in the exposed cohort. COPD accounted for 59.7% of deaths for current use of roflumilast, 51.1% during recent use, and 60.3% during past use. The proportion of patients in the exposed cohort for each of the other causes of death was slightly lower than or equivalent to the proportion in the unexposed group.

Table 15 Frequency Distribution of Cause of Death by Exposure Status in Norway

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)	185 (4.83)	44 (4.67)	9 (3.05)	XXXX	32 (5.32)
Heart failure (I50)	67 (1.75)	17 (1.80)	5 (1.69)	NA	12 (1.99)
Cardiomyopathy (I42, I44, I45)	XXXX	3 (0.32)	XXXX	NA	XXXX
Cerebrovascular disease (I60-I69)	81 (2.11)	14 (1.49)	3 (1.02)	NA	11 (1.83)
COPD (J44)	1,909 (49.79)	562 (59.66)	176 (59.66)	23 (51.11)	363 (60.30)
Influenza and/or pneumonia (J09-J18)	66 (1.72)	10 (1.06)	4 (1.36)	NA	6 (1.00)
Other acute lower respiratory infections (J20-J22)	XXXX	XXXX	XXXX	NA	NA
Other interstitial pulmonary disease (J84)	20 (0.52)	XXXX	NA	NA	XXXX
Cancer (other than lung cancer) (C00-C97, except C34, C44)	691 (18.02)	128 (13.59)	52 (17.63)	8 (17.78)	68 (11.30)
Other causes	741 (19.33)	152 (16.14)	42 (14.24)	10 (22.22)	100 (16.61)
Cause Not Available	59 (1.54)	9 (0.96)	XXXX	XXXX	6 (1.00)
All-cause mortality	**3834**	**942**	**295**	**45**	**602**

COPD = chronic obstructive pulmonary disease; N = number; NA = not applicable

Note: XXXX: Counts below 3 not shown to comply with the small cells rule to prevent identification of small counts.

Source: Appendix 2 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 in Table 16. The numbers of cancer-related events for roflumilast-exposed and unexposed patients are shown in Table 17.

Hospitalisation for any cause and respiratory disease-related hospitalisation were the secondary outcomes with the highest IR. The crude IRs of respiratory disease-related hospitalisation were almost 2-fold higher for current and recent use compared to never use, possibly related to the higher COPD severity in the exposed patients. The crude IRs of major cardiovascular events were similar for current and never use.

Table 16 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in Norway

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)
Hospitalisation for any cause	940 (1158)	811.23 (760.99, 864.78)	95 (109)	867.27 (709.29, 1060.44)	458 (948)	482.69 (440.44, 528.98)	6679 (13875)	481.34 (469.93, 493.02)
Respiratory disease-related hospitalisation	763 (1527)	499.55 (465.33, 536.28)	67 (133)	500.91 (394.24, 636.42)	449 (1504)	298.52 (272.14, 327.45)	5144 (19884)	258.70 (251.72, 265.86)
Major cardiovascular events[a]	101 (2800)	36.07 (29.68, 43.83)	12 (221)	54.23 (30.80, 95.49)	151 (3538)	42.67 (36.38, 50.05)	1147 (30807)	37.23 (35.14, 39.45)
Arrhythmia[b]	3 (2965)	10.12 (3.26, 31.37)	0 (232)	NC	10 (3901)	25.63 (13.79, 47.64)	71 (33119)	21.44 (16.99, 27.05)
Myocardial infarction	56 (2876)	19.47 (14.98, 25.30)	5 (225)	22.16 (9.22, 53.24)	68 (3738)	18.19 (14.34, 23.07)	442 (32274)	13.69 (12.48, 15.03)
Cerebral infarction	11 (2953)	3.72 (2.06, 6.72)	XXXX	4.31 (0.61, 30.62)	24 (3858)	6.22 (4.17, 9.28)	232 (32748)	7.08 (6.23, 8.06)
Heart failure	28 (2939)	9.52 (6.58, 13.80)	7 (229)	30.48 (14.53, 63.93)	54 (3801)	14.20 (10.88, 18.55)	407 (32555)	12.50 (11.34, 13.78)
Pulmonary embolism[b]	16 (2948)	54.26 (33.24, 88.56)	XXXX	86.45 (21.62, 345.66)	32 (3848)	83.16 (58.81, 117.59)	131 (33047)	39.64 (33.40, 47.04)
Hospitalisation due to diarrhoea of non-infectious origin[b]	14 (2955)	47.36 (28.05, 79.97)	XXXX	86.28 (21.58, 345.00)	10 (3882)	25.75 (13.86, 47.86)	79 (33125)	23.85 (19.13, 29.73)
Abnormal, unexplained weight loss[b]	9 (2943)	30.58 (15.91, 58.77)	0 (232)	NC	7 (3912)	17.89 (8.53, 37.53)	70 (33060)	21.17 (16.75, 26.76)
New diagnosis of depression	3 (2953)	1.02 (0.33, 3.15)	0 (231)	NC	4 (3879)	1.03 (0.39, 2.75)	20 (32861)	0.61 (0.39, 0.94)
Death by suicide or hospitalisation for suicide attempt[b]	3 (2963)	10.12 (3.26, 31.39)	0 (231)	NC	4 (3897)	10.26 (3.85, 27.34)	39 (32956)	11.83 (8.65, 16.20)

Table 16 Secondary Outcomes: Number of Events, Person-Years, and Incidence Rates for Current, Recent, and Past Use and for Never Use of Roflumilast in Norway

Outcomes	Current use		Recent use		Past use		Never use	
	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)	N of events (PY)	IR (95% CI)
New diagnosis of tuberculosis, hepatitis B or C or other severe viral hepatitis infection (except hepatitis A)[b]	XXXX	6.78 (1.69, 27.10)	XXXX	43.23 (6.09, 306.86)	3 (3896)	7.70 (2.48, 23.87)	15 (33042)	4.54 (2.74, 7.53)

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

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

Note: XXXX: Counts below 3 not shown to comply with the small cells rule.

CI = confidence interval; IR = incidence rate; N = number; PY = person-years.

Source: Appendix 2 Table 11

For the secondary outcome malignant neoplasms, crude IR estimates were higher in roflumilast exposed compared with unexposed patients (Table 17). Reductions in crude IRs were modest when comparing estimates with no latency to estimates with 1- and 2-years latency for all malignant neoplasms and for haematopoietic/haematological tumours. Haematopoietic tumours accounted for less than 10% of all malignant neoplasms.

Table 17 Number of Malignant Events, Number of Patients at Risk, and Incidence Rates for Ever-Versus-Never Use of Roflumilast in Norway

Outcomes	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)	221 (1479)	869 (6371)	354.33 (310.56, 404.27)	328.40 (307.28, 350.98)
No latency (follow-up limit to 1 year)	49 (1479)	198 (6371)	355.05 (268.34, 469.77)	336.26 (292.54, 386.51)
1 year latency	172 (1281)	593 (4810)	355.73 (306.35, 413.07)	324.05 (298.99, 351.21)
2 years latency	129 (1104)	389 (3656)	360.60 (303.44, 428.52)	316.21 (286.30, 349.25)
Malignant neoplasms - solid tumours				
No latency (new diagnosis)	213 (1479)	838 (6371)	340.72 (297.90, 389.69)	315.99 (295.31, 338.13)
No latency (follow-up limit to 1 year)	48 (1479)	188 (6371)	347.80 (262.10, 461.52)	319.10 (276.60, 368.14)
1 year latency	165 (1281)	574 (4814)	340.24 (292.09, 396.32)	312.78 (288.21, 339.44)
2 years latency	124 (1105)	379 (3666)	345.32 (289.59, 411.78)	306.95 (277.55, 339.46)
Malignant neoplasms - haematopoietic / haematological tumours				
No latency (new diagnosis)	9 (1,479)	39 (6,371)	13.71 (7.13, 26.35)	14.00 (10.23, 19.16)
No latency (follow-up limit to 1 year)	XXXX	10 (6,371)	7.17 (1.01, 50.87)	16.78 (9.03, 31.19)
1 year latency	8 (1,309)	26 (5,023)	15.54 (7.77, 31.06)	13.13 (8.94, 19.28)
2 years latency	6 (1,146)	17 (3,944)	15.55 (6.99, 34.62)	12.45 (7.74, 20.02)

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

Crude rate is per 1000 PY.

Note: XXXX: Counts below 3 not shown to comply with the small cells rule.

CED = cohort entry date; CI = confidence interval; IR = incidence rate; N = number; PY = person-years.

Sources: Appendix 2 Table 12

Table 18 shows the contribution of each of the different diagnosis sub-classes (influenza, pneumonia and other acute lower respiratory infections, bronchitis, emphysema, COPD, asthma, bronchiectasis) to the combined outcome of respiratory disease-related hospitalisation. COPD accounted for 65.7% and 58.2% of hospitalisations in the exposed and unexposed patients, respectively.

Table 18 Distribution of Causes of Respiratory Disease-related Hospitalisation Outcome in Norway

Diagnosis	ICD-10 Code	Unexposed		Exposed		Total	
		N	%	N	%	N	%
Influenza, pneumonia, other acute lower respiratory infections	J09-J22	1984	38.57	413	32.29	2397	37.32
Bronchitis, not specified as acute or chronic; Simple and mucopurulent chronic bronchitis; Unspecified chronic bronchitis[a]	J40-J42, J47	18	0.35	6	0.47	24	0.37
Emphysema	J43	46	0.89	11	0.86	57	0.89
COPD	J44	2993	58.18	840	65.68	3833	59.68
Asthma; Status asthmaticus	J45-J46	103	2.00	9	0.70	112	1.74
Total	--	**5144**	**100**	**1279**	**100**	**6423**	**100**

[a] Smallest categories have been combined to comply with the small cell counts rule

COPD = chronic obstructive pulmonary disease; ICD = International Classification of Diseases and Related Health Problems; N = number.

Sources: Appendix 2 Table 13

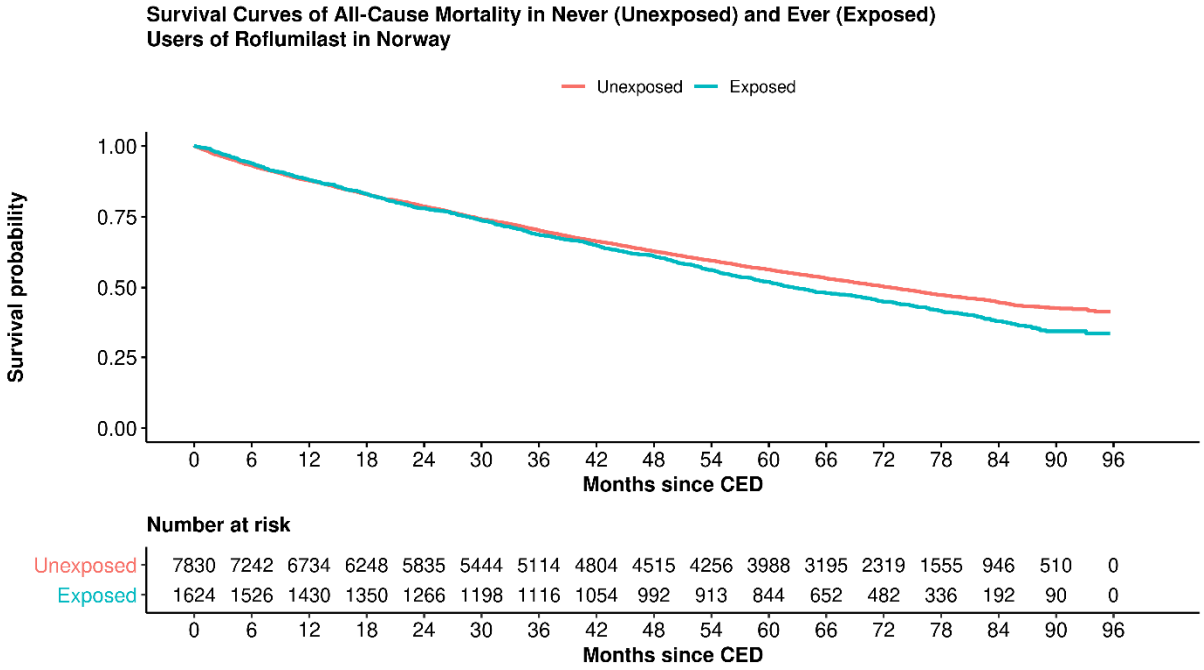
10.4 Outcomes - Main Results

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 4). After approximately 36 months of follow up, the mortality 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 4 Survival Curves of All-cause Mortality in Never (Unexposed) and Ever (Exposed) Users of Roflumilast in Norway



CED = cohort entry date.
Source: Appendix 1 Figure 7d

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

Stratified crude MRs and MRRs by exposure categories are presented in Table 19. An elevated estimate of crude MRR was observed for ever-versus-never use (MRR: 1.11, 95% CI: 1.03, 1.20). The highest crude MRR was associated with a cumulative duration up to 3 months.

For roflumilast exposure classified by exposure status at the time of the outcome events (ie, current, recent, and past versus never use), the smallest MRR was seen for current use; there was no risk increase for during current use.

Stratification of crude estimates of mortality rate by time since discontinuation did not show a consistent pattern across strata. In line with the observed higher MRRs during recent use, crude estimates of MRR in the Days 1 to 89 after discontinuation was also elevated. The estimated MRRs for 3 to 12 months and for more than 12 months were elevated and similar to each other.

Table 19 5-Year All-cause MRs and Crude MRRs for Different Exposure Definitions of Roflumilast Exposure Versus No Exposure in Norway

	N at risk	PY	N of events	Crude MR/1000 PY (95% CI)	Crude MRR (95% CI)
Ever use					
Never	7830	28036	3251	115.96 (112.04, 120.01)	1 (Reference)
Ever	1624	6036	779	129.04 (120.29, 138.43)	1.11 (1.03, 1.20)
Cumulative duration					
Up to 3 months	1624	1398	197	140.83 (122.48, 161.93)	1.21 (1.05, 1.40)
3 to 12 months	1297	2746	373	135.82 (122.71, 150.32)	1.17 (1.05, 1.30)
More than 12 months	606	1891	209	110.49 (96.48, 126.53)	0.95 (0.83, 1.10)
Use status					
Current	1624	2623	258	98.34 (87.04, 111.10)	0.85 (0.75, 0.96)
Recent	1262	221	43	194.41 (144.18, 262.14)	1.68 (1.24, 2.27)
Past	1140	3191	478	149.75 (136.91, 163.80)	1.29 (1.17, 1.42)
Time since discontinuation					
Concurrent	1624	2599	256	98.47 (87.12, 111.30)	0.85 (0.75, 0.96)
Up to 3 months (1-89 days)	1289	351	60	170.57 (132.44, 219.68)	1.47 (1.14, 1.90)
3 to 12 months	1112	812	125	153.82 (129.09, 183.29)	1.33 (1.11, 1.59)
More than 12 months	914	2272	338	148.72 (133.68, 165.46)	1.28 (1.15, 1.43)

CI = confidence interval; MR = mortality rate; MRR = mortality rate ratio; N = number; PY = person-years.
Source: Appendix 2 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 are summarised in Table 20. 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. There was no statistically significant association between exposure to roflumilast and mortality for ever-versus-never exposure to roflumilast, with an adjusted HR of 1.00 (95% CI: 0.92, 1.08).

Table 20 Mortality Rates, Crude and Adjusted Hazard Ratios of 5-Year All-Cause Mortality for Ever-Versus-Never Exposure to Roflumilast in Norway

All-cause mortality	
Number of ever exposed (PY)	1624 (6036)
Number of never exposed (PY)	7830 (28036)
Number of events (ever exposed)	779
Number of events (never exposed)	3251
Mortality rate[a] ever exposed (95% CI)	129.04 (120.29, 138.43)
Mortality rate[a] never exposed (95% CI)	115.96 (112.04, 120.01)
Crude HR (95% CI)	1.06 (0.98, 1.15)

Table 20 Mortality Rates, Crude and Adjusted Hazard Ratios of 5-Year All-Cause Mortality for Ever-Versus-Never Exposure to Roflumilast in Norway

All-cause mortality	
Adjusted [b] HR (95% CI)	1.00 (0.92, 1.08)

[a] Mortality rate estimates per 1000 PY at risk

[b] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; PS = propensity score; PY = person-year.

Sources: Appendix 2 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 21. Adjustment for markers of COPD severity and morbidity beyond the PS matching at baseline consistently reduced all HRs across all exposure categories. After adjustment, there were statistically significantly elevated HRs during recent and past use. For current use, results indicate no increased risk.

Table 21 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality for Current, Recent, and Past Use of Roflumilast Versus Never Use in Norway

All-cause mortality	**Never (reference)**	**Current**	**Recent**	**Past**
Deaths (PY)	3251 (28036)	258 (2623)	43 (221)	478 (3191)
N at risk	7830	1624	1262	1140
MR/1000 PY (95% CI)	115.96 (112.04, 120.01)	98.34 (87.04, 111.10)	194.41 (144.18, 262.14)	149.75 (136.91, 163.80)
Crude HR (95% CI)	1 (reference)	0.76 (0.67, 0.87)	1.51 (1.11, 2.05)	1.30 (1.18, 1.43)
Adjusted[a] HR (95% CI)	1 (reference)	0.77 (0.67, 0.87)	1.42 (1.04, 1.93)	1.15 (1.04, 1.27)

[a] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years

Sources: Appendix 2 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 22. 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, except > 12 months, which remained similar. No statistically

significant elevation of risk for any of the cumulative exposure duration categories was observed in the adjusted analyses.

Table 22 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality Associated with Cumulative Exposure to Roflumilast Versus Never Use in Norway

All-cause mortality	Never (reference)	Up to 3 months	3 to 12 months	> 12 months
Deaths (PY)	3251 (28036)	197 (1398)	373 (2746)	209 (1891)
N at risk	7830	1624	1297	606
MR/1000 PY (95% CI)	115.96 (112.04, 120.01)	140.83 (122.48, 161.93)	135.82 (122.71, 150.32)	110.49 (96.48, 126.53)
Crude HR (95% CI)	1 (reference)	1.11 (0.96, 1.28)	1.14 (1.03, 1.28)	0.91 (0.79, 1.04)
Adjusted[a] HR (95% CI)	1 (reference)	0.92 (0.79, 1.07)	1.10 (0.98, 1.23)	0.91 (0.79, 1.05)

[a] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years

Source: Appendix 2 Table 17

Crude and adjusted HRs of 5-year all-cause mortality associated with cumulative exposure duration of 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 in Table 23.

No statistically significant elevation of risk for any of the cumulative exposure duration categories was observed in the adjusted analyses.

Table 23 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 in Norway

All-cause mortality	Never (reference)	< 3 months	3 to 12 months	> 12 to 24 months	> 24 months
Deaths (PY)	3251 (28036)	197 (1398)	373 (2746)	92 (797)	117 (1094)
N at risk	7830	1624	1297	606	456
Crude HR (95% CI)	1 (reference)	1.11 (0.96, 1.28)	1.15 (1.03, 1.28)	0.96 (0.78, 1.19)	0.87 (0.72, 1.04)
Adjusted[a] HR (95% CI)	1 (reference)	0.92 (0.79, 1.07)	1.10 (0.98, 1.23)	0.97 (0.79, 1.20)	0.87 (0.72, 1.05)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score

Sources: Appendix 2 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 24 presents unadjusted and adjusted HRs of 5-year all-cause mortality associated with time since roflumilast exposure discontinuation versus never use. The adjustment for variables related to COPD severity and morbidity reduced the HRs across all categories, except for the concurrent category.

The adjusted HR for the concurrent use showed no increased risk. An increase in risk that was observed after discontinuation of roflumilast that reached statistical significance after 3 months.

Table 24 Crude and Adjusted Hazard Ratios of 5-Year All-cause Mortality Associated With Time Since Discontinuation of Roflumilast Versus Never Use in Norway

All-cause mortality	Concurrent	Up to 3 months	3 to 12 months	> 12 months
Deaths (PY)	256 (2599)	60 (351)	125 (812)	338 (2272)
N at risk	1624	1289	1112	914
MR/1000 PY (95% CI)	98.47 (87.12, 111.30)	170.57 (132.44, 219.68)	153.82 (129.09, 183.29)	148.72 (133.68, 165.46)
Crude HR (95% CI)	0.77 (0.67, 0.87)	1.31 (1.01, 1.70)	1.31 (1.09, 1.57)	1.30 (1.16, 1.46)
Adjusted[a] HR (95% CI)	0.77 (0.68, 0.88)	1.23 (0.95, 1.60)	1.20 (1.00, 1.45)	1.14 (1.01, 1.28)

[a] Adjusted for age + sex +country specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; MR = mortality rate; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 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 25 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 trend showing decreasing risk of roflumilast exposure from the first quintile (lower PS) with the lowest risk in the fifth quintile (highest PS). The HR for the fifth quintile showed no increased risk.

Table 25 Adjusted Hazard Ratios of 5-Year All-cause Mortality for Ever-Versus-Never Use of Roflumilast Stratified by PS Quintile in Norway

Propensity score quintiles	Adjusted[a] HR (95% CI)
First quintile	1.29 (1.05, 1.58)
Second quintile	1.02 (0.84, 1.24)
Third quintile	1.19 (0.99, 1.43)
Fourth quintile	0.97 (0.80, 1.16)
Fifth quintile	0.79 (0.67, 0.93)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching in any of the 5 PS quintiles (Table 9) + markers of COPD severity and morbidity (Final CSR Table 10).

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSR = clinical study report; HR = hazard ratio; PS = propensity score

Sources: Appendix 2 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 with the same set of covariates as for the primary outcome.

Crude and adjusted HRs for secondary outcomes for current, recent, and past use versus never use of roflumilast are presented in Table 26.

Whereas adjustment for relevant covariates consistently reduced the risk estimates for 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 increase in risk for current use, with a similar magnitude of increased risk for recent and past use.

A numerical increase in the risk of new diagnosis of depression was observed. The risk of abnormal and unexplained weight loss showed elevated HRs for current and past use of roflumilast. A statistically significant increased risk was observed for hospitalisation due to diarrhoea for current use, a known side effect of roflumilast. A statistically significant increase was observed for past use of roflumilast for hospitalisations due to myocardial infarction. Similarly, significant increases were seen for past use for hospitalisations due to pulmonary embolism and for recent use for new diagnoses of tuberculosis or hepatitis B or C or other severe viral hepatitis (except hepatitis A). Due to the small number of events for some endpoints and categories, CIs were very wide and should be interpreted with caution.

Table 26 Crude and Adjusted Hazard Ratios for Secondary Outcomes for Current, Recent, and Past Use Versus Never Use of Roflumilast in Norway

	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	1.27 (1.17, 1.37)	1.36 (1.07, 1.74)	1.49 (1.35, 1.64)	1.20 (1.11, 1.30)	1.44 (1.12, 1.84)	1.45 (1.31, 1.60)
Hospitalisation for any cause	1.18 (1.10, 1.26)	1.43 (1.17, 1.76)	1.32 (1.20, 1.46)	1.14 (1.06, 1.22)	1.42 (1.15, 1.75)	1.27 (1.15, 1.40)
New diagnosis of depression	1.44 (0.42, 4.93)	NC	1.96 (0.65, 5.89)	1.53 (0.43, 5.40)	NC	1.90 (0.60, 5.99)
Death by suicide or hospitalisation for suicide attempt	0.79 (0.24, 2.57)	NC	0.89 (0.32, 2.51)	0.73 (0.22, 2.42)	NC	0.81 (0.28, 2.35)
Hospitalisation due to diarrhoea of non-infectious origin	1.86 (1.05, 3.32)	3.92 (0.93, 16.42)	1.10 (0.57, 2.14)	2.03 (1.12, 3.67)	3.73 (0.88, 15.86)	1.05 (0.53, 2.07)
Abnormal and unexplained weight loss	1.36 (0.67, 2.74)	NC	0.88 (0.40, 1.92)	1.64 (0.80, 3.37)	NC	1.04 (0.47, 2.31)
Hospitalisations due to major cardiovascular events	0.69 (0.56, 0.85)	1.11 (0.63, 1.98)	1.19 (1.00, 1.41)	0.72 (0.58, 0.89)	1.11 (0.62, 1.97)	1.14 (0.95, 1.36)
Hospitalisations due to arrhythmia	0.45 (0.14, 1.43)	NC	1.21 (0.62, 2.37)	0.42 (0.13, 1.36)	NC	1.00 (0.50, 2.00)
Hospitalisations due to myocardial infarction	1.06 (0.80, 1.41)	1.24 (0.51, 3.03)	1.41 (1.09, 1.83)	1.07 (0.80, 1.44)	1.23 (0.50, 3.01)	1.32 (1.01, 1.73)
Hospitalisations due to cerebral infarction	0.53 (0.29, 0.96)	0.53 (0.07, 3.80)	0.90 (0.59, 1.37)	0.58 (0.31, 1.08)	0.53 (0.07, 3.87)	0.87 (0.56, 1.33)
Hospitalisations due to heart failure	0.62 (0.42, 0.91)	1.84 (0.86, 3.93)	1.20 (0.90, 1.59)	0.67 (0.45, 0.99)	1.85 (0.86, 3.99)	1.11 (0.83, 1.50)
Hospitalisations due to pulmonary embolism	1.09 (0.64, 1.86)	1.71 (0.41, 7.05)	2.12 (1.43, 3.13)	1.18 (0.68, 2.03)	1.78 (0.43, 7.41)	2.11 (1.41, 3.17)

Table 26 Crude and Adjusted Hazard Ratios for Secondary Outcomes for Current, Recent, and Past Use Versus Never Use of Roflumilast in Norway

	Crude HRs (95% CI)			Adjusted [a] HRs (95% CI)		
	Current use	**Recent use**	**Past use**	**Current use**	**Recent use**	**Past use**
New diagnoses of tuberculosis or hepatitis B or C or other severe viral hepatitis (except hepatitis A)	1.73 (0.39, 7.59)	9.34 (1.14, 76.31)	1.64 (0.47, 5.70)	1.59 (0.34, 7.46)	12.35 (1.34, 113.59)	1.87 (0.52, 6.78)

[a] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 9). 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; HR = hazard ratio; NC = not calculated; PS = propensity score.

Sources: Appendix 2 Table 22

Hospitalisation for suicide attempt showed no risk increase in data from NOR (Table 26), as across all countries, for current use. This outcome was explored in more detail. Table 27 presents detailed results on the association of roflumilast exposure with hospitalisation for suicide attempt excluding and including patients with prior suicide attempt. Overall, the number of suicide attempts was very small, and excluding patients with prior suicide attempt reduced the number of events only by a very small number. The estimated hazard ratios were below 1 for all analyses, due to the small number of events, CIs were very wide, and none of the risk estimates were statistically significant. For patients with recent use of roflumilast, no events were identified.

Table 27 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 in Norway

Exposure	N events	PY	Crude IR (95% CI)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Excluding patients with prior suicide attempt					
Current use	3	2963	10.12 (3.26, 31.39)	0.79 (0.24, 2.57)	0.73 (0.22, 2.42)
Recent use	0	231	NC	NC	NC
Past use	4	3897	10.26 (3.85, 27.34)	0.89 (0.32, 2.51)	0.81 (0.28, 2.35)
Never use	39	32956	11.83 (8.65, 16.20)	1.00 (Reference)	1.00 (Reference)
Including patients with prior suicide attempt					
Current use	3	2973	10.09 (3.25, 31.29)	0.77 (0.24, 2.50)	0.72 (0.22, 2.38)
Recent use	0	233	NC	NC	NC
Past use	4	3912	10.23 (3.84, 27.24)	0.87 (0.31, 2.44)	0.78 (0.27, 2.27)
Never use	40	33235	12.04 (8.83, 16.41)	1.00 (Reference)	1.00 (Reference)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9). 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; HR = hazard ratio; IR = incidence rate; N = number; NC = not calculated; PS = propensity score; PY = person-years.

Sources: Appendix 2 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 28. The risk of cancer was not significantly elevated for any latency category.

Table 28 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 in Norway

Outcomes	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
New diagnosis of malignant neoplasm with no latency	1.03 (0.88, 1.21)	1.06 (0.91, 1.23)
New diagnosis of malignant neoplasm with 1 year latency	0.92 (0.77, 1.11)	0.96 (0.81, 1.15)
New diagnosis of malignant neoplasm with 2 years latency	0.97 (0.78, 1.21)	1.04 (0.85, 1.27)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9). 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; HR = hazard ratio; PS = propensity score.

Sources: Appendix 2 Table 24

Malignancies analysed by malignant neoplasms into solid and haematopoietic tumours were performed (Table 29). 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 haematopoietic tumours, no significant results were seen, and the CIs were generally wide.

Table 29 Crude and Adjusted Hazard Ratios for Solid and Haematopoietic Tumours for Ever-Versus-Never Use of Roflumilast in Norway

Latency	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Solid tumours		
No latency	0.94 (0.81, 1.09)	0.94 (0.80, 1.09)
1-year latency	0.96 (0.80, 1.14)	0.92 (0.76, 1.11)
2-year latency	1.02 (0.83, 1.25)	0.95 (0.76, 1.19)
Haematopoietic tumours		
No latency	1.10 (0.57, 2.12)	1.14 (0.57, 2.28)
1-year latency	1.18 (0.53, 2.61)	1.04 (0.44, 2.44)
2-year latency	1.24 (0.49, 3.16)	1.11 (0.40, 3.06)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9). 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; HR = hazard ratio; PS = propensity score.

Sources: Appendix 2 Table 25

The distributions of type of solid or haematopoietic tumours were analysed (Table 30 and Table 31, respectively). Among solid tumours, neoplasms of bronchus and lung were the most frequent and contributed 41.8% of all tumours in the exposed and 34.2% in the unexposed group (p = 0.196). For haematopoietic tumours, the number of each tumour type was very small in the exposed (N = 8) and unexposed groups (N = 26). No accumulation of a particular type of haematopoietic tumour was observed in association with roflumilast exposure (global p = 0.768).

Table 30 Number and Percentage of Solid Tumours by Tumour Type and Exposure Status in Norway

Tumour type	Diagnosis code	Unexposed N (%)	Exposed N (%)	P-value[a]
Malignant neoplasms of lip, oral cavity, and pharynx	C00-C14	8 (1.40)	3 (1.90)	0.974
Malignant neoplasms of digestive organs	C15-C26	147 (25.65)	30 (18.99)	0.062
Malignant neoplasms of respiratory and intrathoracic organs	C30-C33, C37-C39	5 (0.87)	4 (2.53)	0.230
Malignant neoplasms of bronchus and lung	C34	196 (34.21)	66 (41.77)	0.196
Malignant neoplasms of bone and articular cartilage	C40-C41	XXXX	XXXX	1.000
Melanoma and other malignant neoplasms of skin	C43	19 (3.32)	4 (2.53)	0.747
Malignant neoplasms of mesothelial and soft tissue	C45-C49	4 (0.70)	XXXX	0.875

Table 30 Number and Percentage of Solid Tumours by Tumour Type and Exposure Status in Norway

Tumour type	Diagnosis code	Unexposed N (%)	Exposed N (%)	P-value[a]
Malignant neoplasms of breast	C50	25 (4.36)	11 (6.96)	0.312
Malignant neoplasms of female genital organs	C51-C58	10 (1.75)	XXXX	0.486
Malignant neoplasms of male genital organs	C60-C63	73 (12.74)	22 (13.92)	0.939
Malignant neoplasms of urinary tract	C64-C68	52 (9.08)	18 (11.39)	0.573
Malignant neoplasms of eye, brain, and other parts of central nervous system	C69-C72	14 (2.44)	XXXX	0.247
Malignant neoplasms of thyroid and other endocrine glands	C73-C75	5 (0.87)	XXXX	1.000
Malignant neoplasms of ill-defined, other secondary and unspecified sites	C76-C80	15 (2.62)	XXXX	0.445
Total	-	XXXX	XXXX	-

[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 = 0.332

Note: XXXX: Counts below 3 not shown to comply with the small cells rule to prevent identification of small counts.

N = number of patients.

Source: Appendix 2 Table 26

Table 31 Number and Percentage of Haemopoietic Tumours by Tumour Type and Exposure Status in Norway

Tumour type	Diagnosis code	Unexposed N (%)	Exposed N (%)	P-value[a]
Hodgkin lymphoma	C81	XXXX	XXXX	1.000
Non-follicular lymphoma	C83	6 (27.27)	4 (100.00)	0.309
Mature T/NK-cell lymphomas	C84	XXXX	XXXX	1.000
Other specified and unspecified types of non-Hodgkin lymphoma	C85	XXXX	XXXX	0.960
Multiple myeloma and malignant plasma cell neoplasms	C90	5 (22.73)	XXXX	1.000
Lymphoid leukaemia	C91	7 (31.82)	XXXX	0.716
Myeloid leukaemia	C92	4 (18.18)	XXXX	1.000
Total	-	26	8	-

[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 = 0.768.

Note: XXXX: Counts below 3 not shown to comply with the small cells rule.

N = number of patients; NK = natural killer

Source: Appendix 2 Table 27

In the exploratory analyses of cause-specific mortality, a decrease in risk was seen for cancer-related deaths. The risk of cardiovascular disease-related deaths, respiratory-disease related deaths, and deaths for other causes was not elevated; the CIs including 1 (Table 32).

Table 32 Crude and Adjusted Hazard Ratios for Exploratory Cause-Specific Mortality Outcomes for Ever-Versus-Never Use of Roflumilast in Norway

Exploratory outcomes	Crude HR (95% CI)	Adjusted[a] HR (95% CI)
Cancer-related deaths	0.56 (0.42, 0.76)	0.60 (0.43, 0.84)
Cardiovascular disease-related deaths	1.04 (0.81, 1.33)	1.11 (0.84, 1.46)
Respiratory disease-related deaths	1.24 (1.1.4, 1.36)	1.09 (0.98, 1.20)
Other causes	0.92 (0.77, 1.09)	0.84 (0.69, 1.03)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; PS = propensity scores.

Source: Appendix 2 Table 28

10.5 Additional Analyses - Sensitivity Analyses

10.5.1 Sensitivity Analyses for the Primary Outcome

Several sensitivity analyses were conducted 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 (Table 41). Ever-exposed patients with a mortality event within the 3 or 12 months after CED were excluded together with their controls in this analysis. The sensitivity analysis resulted in slightly higher point estimates for the adjusted HR compared to the main analysis.

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 risks observed for current, recent, and past roflumilast users versus never use (Table 42).

No gap extension and 100% gap extension showed comparable point estimates and similar pattern to that observed in the main analysis of current and past use versus never use described in Table 21. No gap extension and 100% gap extension raised the adjusted HR estimate only for recent use of roflumilast.

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 43). There was a significantly elevated risk of mortality for each category of number of dispensations versus never use except for > 10 dispensations of roflumilast for which the risk was significantly reduced versus never use.

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

For a better understanding, the analysis of ever vs never use was stratified by duration of cumulative use by categories of ≤ 12 months, > 12 to 24 months, and > 24 months (Table 33). The mortalities were similar across cumulative exposure categories (≤ 12 months, > 12 to 24 months and > 24 months) and did not indicate an elevated risk in any specific exposure period.

Table 33 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 in Norway

All-cause mortality	**≤ 12 months**	**> 12 to 24 months**	**> 24 months**
Deaths (PY)	570 (4145)	92 (797)	117 (1094)
N at risk	1624	606	456
Crude HR (95% CI)	1.13 (1.04, 1.24)	0.96 (0.78, 1.19)	0.87 (0.72, 1.04)
Adjusted [a] HR (95% CI)	1.03 (0.94, 1.13)	0.97 (0.78, 1.20)	0.87 (0.72, 1.05)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = Hazard ratio; N = number; PS = propensity score; PY = person-years

Sources: Appendix 2 Table 29

10.5.1.5 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 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 34). The HRs observed for current use of roflumilast was below 1 for any of the durations of use.

Adjusted HRs showed statistically significant increases in risk in past use for all 3 cumulative exposures and recent use for < 12 months and > 24 months. However, the very small number

of events and number of patients at risk in the recent use stratum makes an interpretation difficult.

Table 34 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 in Norway

All-cause mortality		≤ 12 months			> 12 to 24 months			> 24 months		
	Never (reference)	Current	Recent	Past	Current	Recent	Past	Current	Recent	Past
Deaths (PY)	3251 (28036)	118 (1089)	35 (176)	417 (2878)	54 (559)	XXXX	36 (215)	86 (974)	XXXX	25 (97)
N at risk	7830	1624	1082	964	606	149	115	456	157	107
Crude HR (95% CI)	1 (reference)	0.77 (0.63, 0.93)	1.52 (1.08, 2.14)	1.26 (1.14, 1.40)	0.81 (0.62, 1.07)	0.77 (0.19, 3.08)	1.40 (1.01, 1.95)	0.73 (0.59, 0.91)	2.11 (0.94, 4.73)	2.05 (1.38, 3.05)
Adjusted [a] HR (95% CI)	1 (reference)	0.79 (0.65, 0.96)	1.44 (1.03, 2.03)	1.14 (1.03, 1.27)	0.84 (0.63, 1.10)	0.88 (0.22, 3.51)	1.49 (1.07, 2.08)	0.79 (0.64, 0.98)	2.09 (0.93, 4.69)	1.75 (1.17, 2.62)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR Table 10). The models assume different baseline hazards for each stratum; strata were defined as PS quintiles per cohort entry year in each country.

Note: XXXX: Counts below 3 not shown to comply with the small cells rule to prevent identification of small counts.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 30

10.5.1.6 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 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 35).

Adjusted HRs did not show a consistent time-related pattern. No statistically significant increase in HR was observed across strata up to 4 years of follow up.

Table 35 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 in Norway

Follow-up time period from index date[a]	Adjusted[b] HR (95% CI) for all-cause mortality
Never use (reference)	1.00 (Reference)
Ever use: ≤ 1 year	0.89 (0.76, 1.04)
Ever use: > 1 to 2 years	0.99 (0.83, 1.18)
Ever use: > 2 to 3 years	0.99 (0.82, 1.18)
Ever use: > 3 to 4 years	0.89 (0.73, 1.09)
Ever use: > 4 to 5 years	1.34 (1.12, 1.62)
Ever use: > 5 years	1.19 (1.00, 1.43)

[a] Analyses were conducted utilising 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.

[b] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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.

CED = cohort entry date; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSR = clinical study report; HR = hazard ratio; PS = propensity score.

Sources: Appendix 2 Table 37

10.5.1.7 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 NOR, patients were censored after their first discontinuation of roflumilast.

With censoring after first discontinuation, none of the adjusted HRs for the cumulative exposure categories showed any significant increase in mortality (Table 36).

Table 36 Sensitivity Analysis of 5-Year 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 Norway

All-cause mortality	Never (reference)	Up to 3 months	3 to 12 months	> 12 to 24 months	> 24 months
Deaths (PY)	920 (7135)	38 (338)	52 (462)	38 (373)	65 (852)
N at risk	7830	1,624	1,158	426	310
Crude HR (95% CI)	1 (reference)	0.60 (0.43, 0.85)	0.65 (0.48, 0.88)	0.79 (0.55, 1.15)	0.55 (0.40, 0.75)
Adjusted[a] HR (95% CI)	1 (reference)	0.59 (0.42, 0.83)	0.61 (0.45, 0.83)	0.69 (0.48, 1.00)	0.47 (0.34, 0.65)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 42

10.5.1.8 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 37).

The ITT analysis results were quite similar to the results of the main analyses.

Table 37 Intention-to-treat Sensitivity Analysis for 5-Year All-cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast in Norway

Use status	N at risk	PY	N of events	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
Never	6588	25004	2820	1.00 (Reference)	1.00 (Reference)
Ever	1364	5130	633	1.05 (0.96, 1.15)	0.99 (0.91, 1.09)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 38

10.5.1.9 HDPS Sensitivity Analysis of the Primary Outcome

Results of the HDPS matching are presented in Appendix 7 Table 111.

In the HDPS-matched patients, the mortality rate was higher in the roflumilast-exposed cohort compared to the unexposed cohort (Table 38). The adjusted HR indicated no increase in mortality for the roflumilast-exposed cohort, and it was similar in the analyses using conventional PS matching (Table 20).

Table 38 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	Norway
Number of ever exposed (PY)	1603 (7050)
Number of never exposed (PY)	7502 (31643)
Number of events (ever exposed)	925
Number of events (never exposed)	3659
Mortality rate[a] ever exposed (95% CI)	131.20 (123.01, 139.93)
Mortality rate[a] never exposed (95% CI)	115.64 (111.95, 119.44)
Crude HR (95% CI)	1.02 (0.94, 1.11)
Adjusted[b] HR (95% CI)	0.99 (0.91, 1.08)

[a] Mortality rate estimates per 1000 PY at risk

[b] Adjusted for age + sex +country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HDPS = high-dimension propensity score; HR = hazard ratio; PS = propensity score; PY = person-years.

Source: Appendix 2 Table 52

10.5.2 Exploratory Analyses

10.5.2.1 Subgroup Analysis by Presence or Absence of Asthma

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 risk, with the CI for patients without asthma is contained within the CI for patients with asthma (Table 44).

10.5.2.2 Further Adjustment of the Cox Model With Imbalanced 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 adjustments resulted in lower or similar adjusted HRs (Table 39), in relation to the main analysis (Table 22 to Table 24).

Table 39 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)
Ever use	
Never	1.00 (Reference)
Ever	0.99 (0.91, 1.08)
Cumulative duration	
Up to 3 months	0.93 (0.80, 1.08)
3 to 12 months	1.08 (0.97, 1.21)
More than 12 months	0.91 (0.78, 1.05)
Use status	
Current	0.76 (0.67, 0.87)
Recent	1.40 (1.03, 1.91)
Past	1.15 (1.04, 1.27)
Time since discontinuation	
Concurrent	0.76 (0.67, 0.87)
Up to 3 months (1-89 days)	1.22 (0.94, 1.58)
3 to 12 months	1.20 (0.99, 1.44)
More than 12 months	1.13 (1.01, 1.28)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR Table 10) + country specific imbalanced covariates at CED-1 (Figure 2). 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; CSR = clinical study report; HR = hazard ratio; PS = propensity score.

Sources: Appendix 2 Table 39

10.5.2.3 Analysis of Hospitalisations Surrounding Roflumilast Discontinuation

Since an increased mortality 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 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 40). 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 as follows: 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.

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 respiratory disease-related hospitalisation increased from 29.0% to 51.6%. Similarly, the percentage of patients with at least 1 all-cause hospitalisation increased from 32.3% to 54.8%. There were high percentages of patients with at least one respiratory disease-related hospitalisation (64.5%) and least one all-cause hospitalisation during any of the 3 time periods. The sum of the patients with hospitalisations during the different time periods exceeding the number given in the last column indicates that many patients were hospitalized in more than one time period.

These findings might indicate a deterioration in health status which triggered the discontinuation of roflumilast leading to the status of recent use and could also be related to the subsequently observed death (Table 40).

Table 40 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 in Norway

	Observed during recent use period	Observed ≤55 days before recent use period	Observed 56-110 days before recent use period	Observed during total maximum of 165 days
Exposed patients who died during recent use period	31	31	31	31
Patients with at least 1 hospitalisation for any cause (including respiratory diseases)	14 (45.16%)	17 (54.84%)	10 (32.26%)	22 (70.97%)
Patients with at least 1 respiratory disease-related hospitalisation	13 (41.94%)	16 (51.61%)	9 (29.03%)	20 (64.52%)

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).
Sources: Appendix 2 Table 40

10.6 Meta-analysis

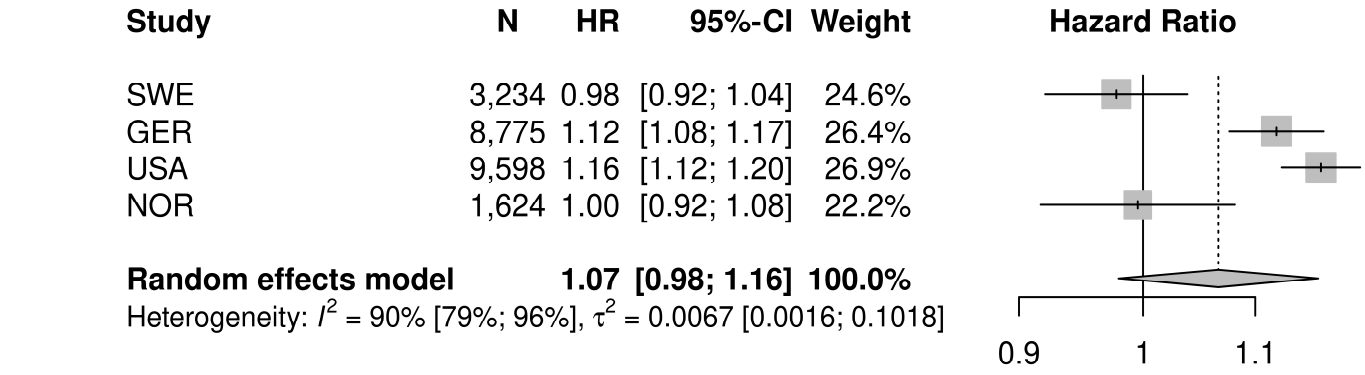
10.6.1 Primary Outcome

In the meta-analysis, considerable between-country heterogeneity of data from GER, SWE, the US, and NOR was observed (I^2=90%; Figure 5), with outputs from GER and the US showing a slightly increased 5-year all-cause mortality for ever-versus-never exposure, no increase in NOR, and a non-significant beneficial effect in SWE. This heterogeneity might be due to the fact that in SWE and NOR, the variable “duration of COPD” was available for inclusion 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 led to a better balance regarding COPD severity between the exposed and unexposed cohort in SWE and NOR.

Analyses by exposure categories (cumulative duration of use, current exposure) showed no consistent evidence of an increased risk of mortality across study countries (Figure 6).

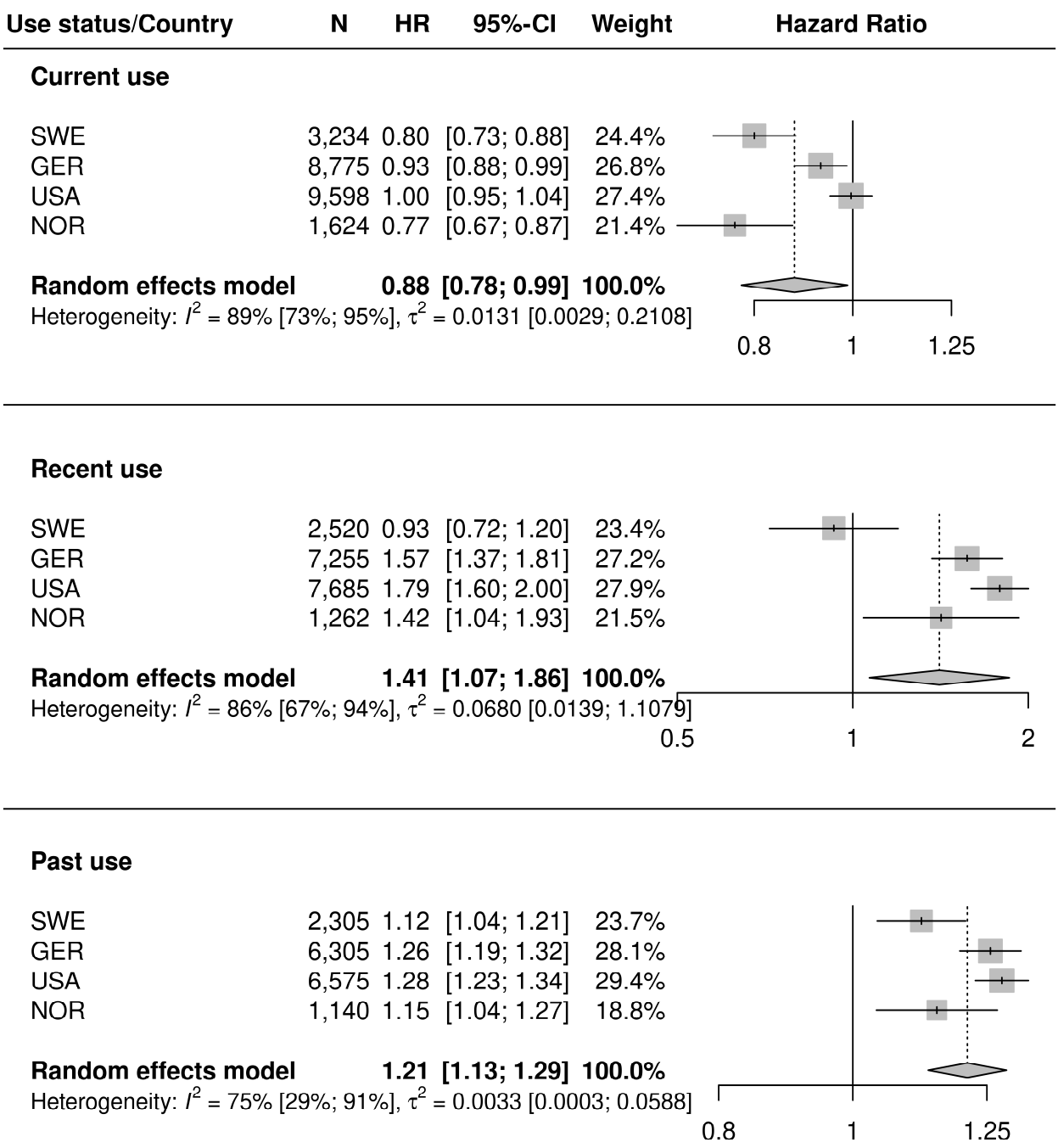
Figure 5 Meta-Analysis Showing the Adjusted Hazard Ratios for 5-Year All-Cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 1

Figure 6 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)



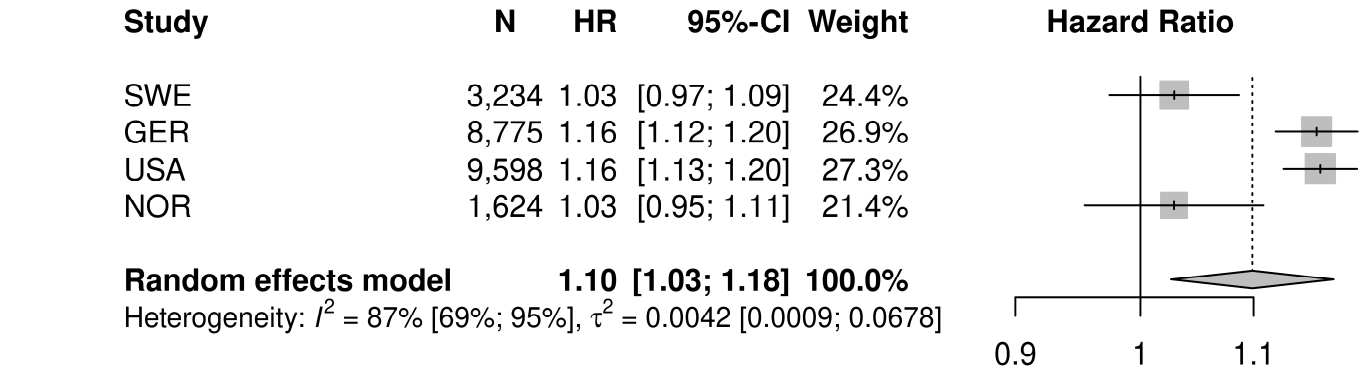
CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, 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 7; the adjusted HRs for hospitalisation for any cause is shown in Figure 8; the adjusted HRs for major cardiovascular events leading to hospitalisation is shown in Figure 9; the adjusted HRs for respiratory disease-related hospitalisation is shown in Figure 10; the adjusted HRs for new diagnosis of malignant neoplasm is shown in Figure 11; and the 5-year all-cause mortality associated with ever-versus-never exposure for HDPS Matching is shown in Figure 12.

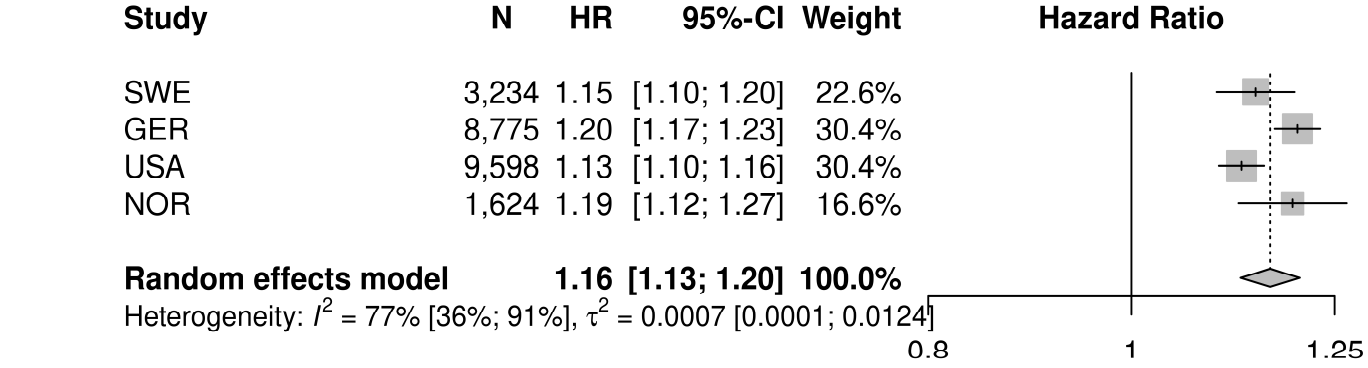
Figure 7 Meta-Analysis Showing the Adjusted Hazard Ratios for All-Cause Mortality Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 5

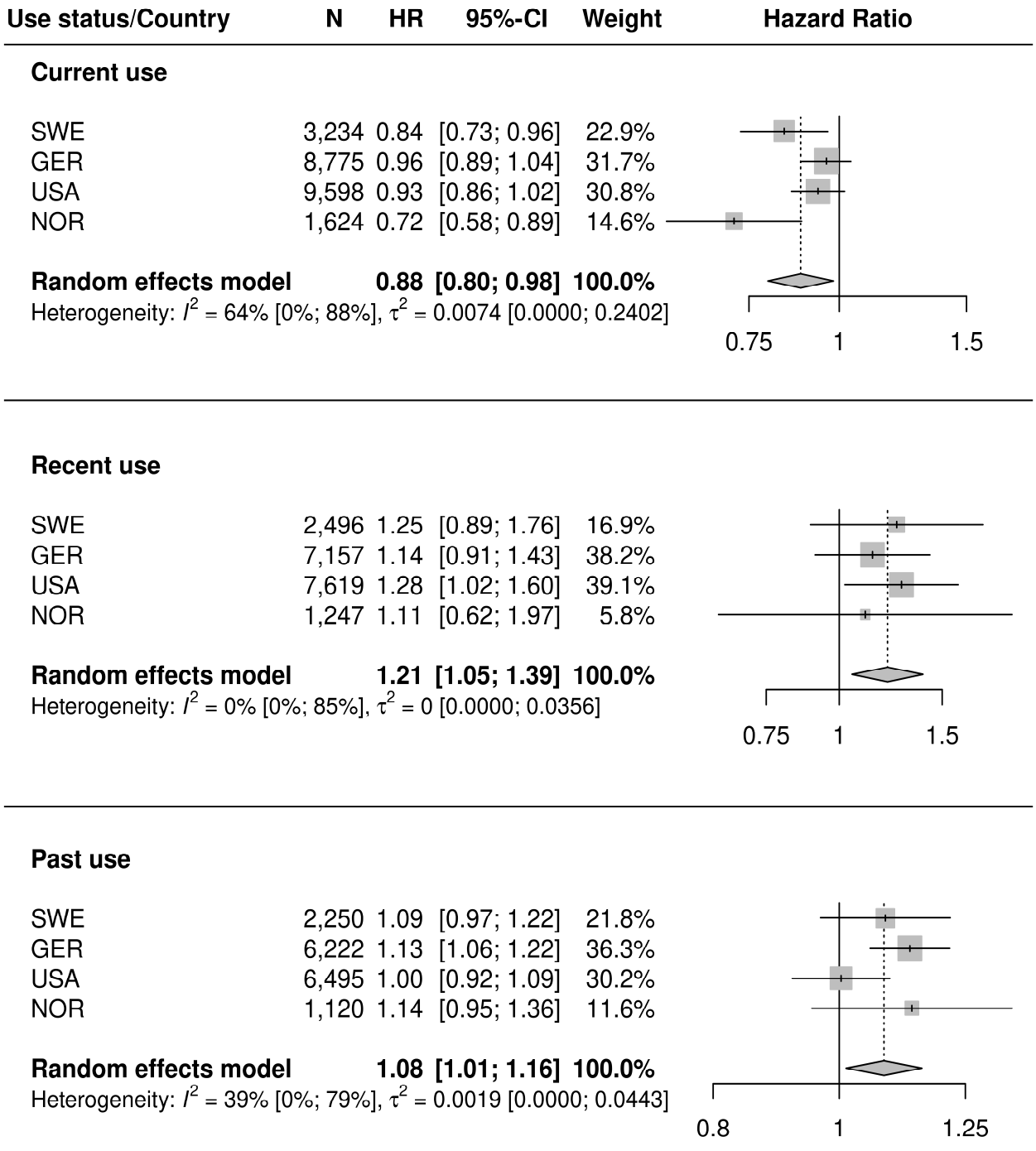
Figure 8 Meta-Analysis Showing the Adjusted Hazard Ratios for Hospitalisation for Any Cause Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 9

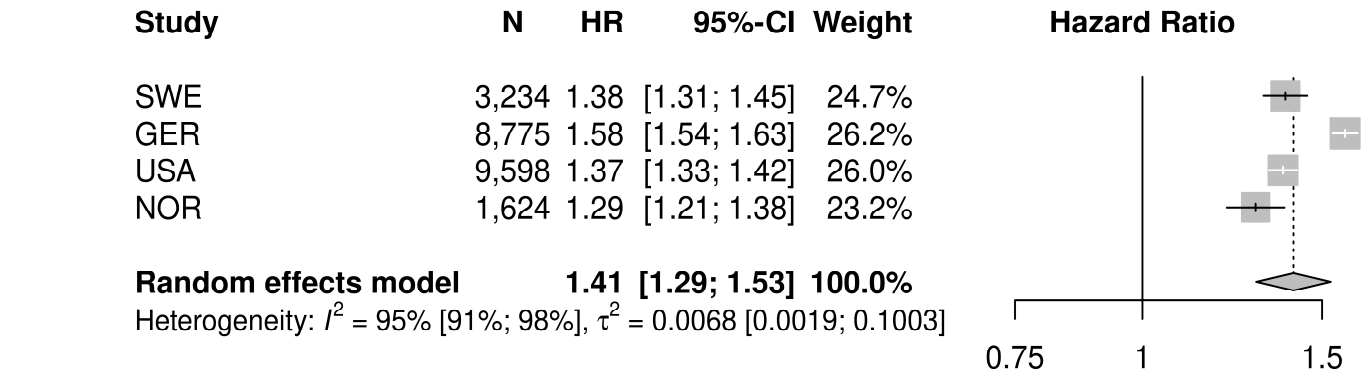
Figure 9 Meta-Analysis Showing the Adjusted Hazard Ratios for Major Cardiovascular Events Leading to Hospitalisation Associated with Use Status (Current, Recent, and Past) Versus Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 13

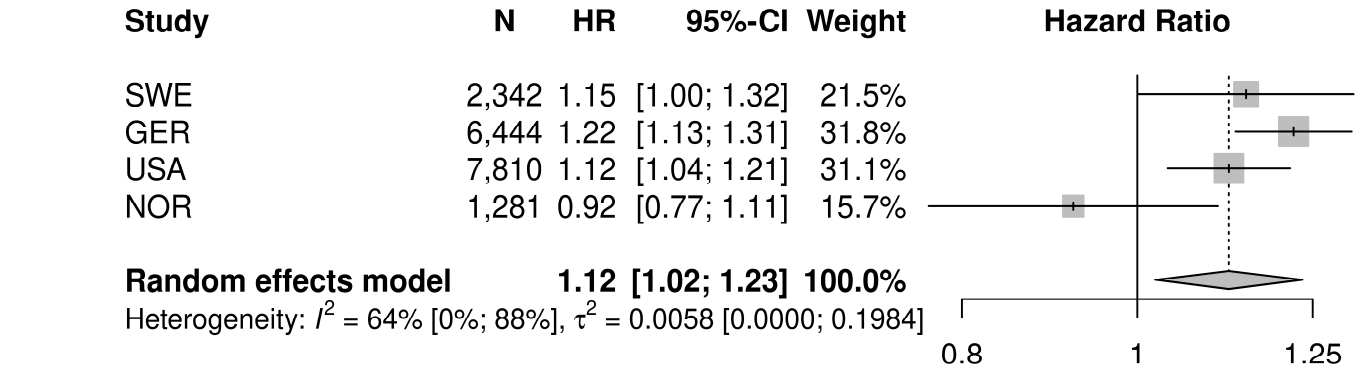
Figure 10 Meta-Analysis Showing the Adjusted Hazard Ratios for Respiratory Disease-related Hospitalisation Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 16

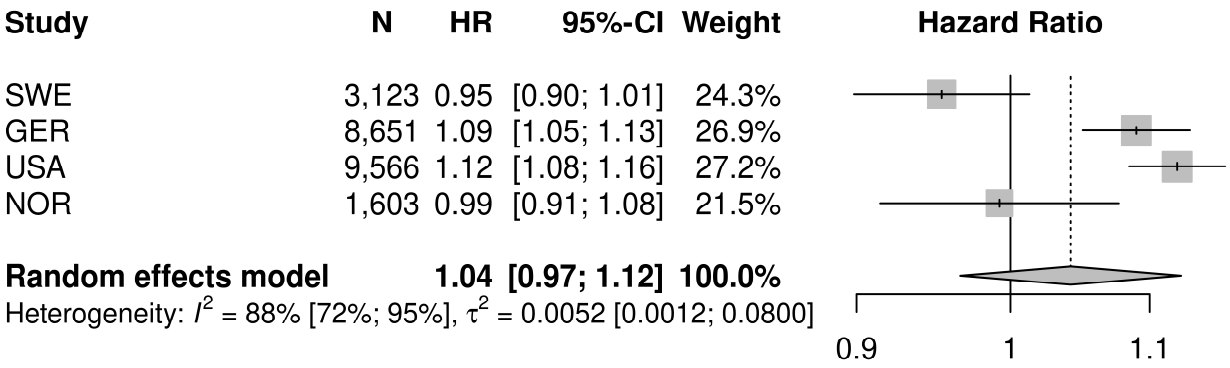
Figure 11 Meta-Analysis Showing the Adjusted Hazard Ratios for New Diagnosis of Malignant Neoplasm (Except Non-Melanoma Skin Cancer) Associated with Ever-Versus-Never Exposure to Roflumilast (Reference) Using Random Effect Models (Main Analysis)



CI = confidence interval; GER = Germany; HR = hazard ratio; N = number of patients; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, Figure 20

Figure 12 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; NOR = Norway; SWE = Sweden; USA = United States.

Source: Appendix 5, 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 4 databases in GER, SWE, the US, and NOR study cohorts of COPD were identified in 2011, 2012, and 2013, roflumilast-treated patients were matched to roflumilast-untreated patients using PS methods. Results for GER, SWE, and the US were reported previously, and this addendum to the Final CSR presents the results of data from NOR for the planned analyses through the end of study follow-up.

Based on the study duration, the potential follow-up for patients in the study was up to 8 years in NOR, and the median follow-up time was approximately 5.0 years in NOR (Table 13), which was similar to the other 3 countries in the study where the average follow-up time was > 4.2 years, including SWE where the median follow-up time was 5.2 years. In NOR, the size of the study population was 1624 exposed and 7830 unexposed patients, which is the smallest population of the 4 studied countries and about half of the SWE study population.

Of all roflumilast-exposed patients in NOR, 18 patients had to be excluded since no matching controls could be found. As seen in each of the other countries, in NOR 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 10; Section 10.1). However, the crude MR in the roflumilast exposed matched and unmatched patients was similar in NOR (Table 11) while in the other countries, the all-cause MRs in the unmatched roflumilast-exposed patients were higher than in the matched roflumilast-exposed patients. In additional analyses conducted to further understand the unmatched roflumilast users compared to the matched roflumilast users included survival curves evaluating time to death, the results for NOR were consistent with the other countries, showing that the survival curves separate after approximately 36 months of follow-up, with a lower probability of survival in the unmatched cohort (Figure 4).

The PS matching within each annual cohort resulted in a similar PS distribution between the exposed and unexposed patients. However, in the matched cohort, despite PS matching, at cohort entry, more patients in the roflumilast-exposed cohort had high PS values, indicating higher COPD severity. As observed in the other countries, some variables in NOR 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, descriptive analysis showed that after matching at CE, 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 lead to an optimal balance and that a baseline imbalance of COPD severity markers was still present. In both NOR and SWE, 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.

Consistent with data presented in the Final CSR for the primary outcome of 5-year all-cause mortality in GER, SWE, and the US, crude MRRs and HRs for the NOR data were elevated for ever-versus-never exposure to roflumilast. After adjustment for age, sex, the country-specific variables imbalanced after PS matching, and for markers of COPD severity and general morbidity, there was no statistically significant difference in the 5-year mortality risk for ever-versus-never exposure to roflumilast in NOR, with an adjusted HR of 1.00 (95% CI: 0.92, 1.08) (Table 20). With further adjustment for covariates that were imbalanced (standardised mean difference >0.1) at 1 year before CED, the HRs for ever-versus-never use of roflumilast were further reduced to 0.99 (95% CI: 0.91, 1.08) in NOR (Table 39), which was consistent with the results seen in SWE where the adjusted HR was 0.96 (95% CI: 0.90, 1.02).

Consistent with the results in GER, SWE, and the US, in analyses of ever-versus-never use of roflumilast with cumulative duration categories ≤ 12 months, > 12 to 24 months, and > 24 months, no consistent pattern of an elevated risk for any particular cumulative duration stratum was apparent in NOR (Table 23).

In NOR, 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 as was seen in SWE and the US (Table 36). For cumulative exposure durations > 24 months, adjusted HR was 0.47 (95% CI: 0.34, 0.65) in NOR while in SWE adjusted HR was 0.98 (95% CI: 0.80, 1.21).

In an ITT analysis conducted 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, results were quite similar to the results of the main analyses, with an adjusted HR of 0.99 (0.91, 1.09) in NOR (Table 37).

In NOR, additional adjustment for covariates imbalanced at 1 year before CED in the analysis using cumulative duration of < 3 months, 3 to 12 months, and > 12 months resulted in minor differences to the main analysis (Table 22, Table 39). In SWE, in this analysis, the adjusted HR for cumulative exposure >12 months was reduced to a statistically non-significant value (HR: 0.92; 95% CI: 0.83, 1.03).

As with the lack of a consistent association of the risk of mortality by increasing roflumilast exposure duration, the analyses by number of roflumilast dispensations did not reveal an association between the risk of mortality and an increasing number of roflumilast dispensations (Table 43). The HR was below 1 for the comparison of ≥ 10 dispensations of roflumilast versus never use. Overall, as was also seen in SWE and the US, 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, the adjusted HR was 0.77 (95% CI: 0.67, 0.87) in NOR (Table 21) which was consistent with the results in SWE where the HR was 0.80 (95% CI: 0.73, 0.88). Concerning the increased risk for recent use, Pharmacovigilance Risk Assessment Committee 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 use and provide “a sensitivity analysis indicating the time to onset of death in the time window of recent use” (see Appendix 3, Table 1). Limitations to this sensitivity analysis are discussed in the Final CSR Section 11.2.

For current use of roflumilast, no elevated risk was observed for any of the durations of use in NOR (Table 34). For recent use, adjusted HRs showed a statistically significant increase for < 12 months in NOR. For past use, adjusted HRs reached statistical significance for all durations in NOR. These findings have to be interpreted given the imbalances of COPD severity observed at CED and their increasing divergence over follow-up time. 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.

Consistent with the data for SWE, in NOR mortality from COPD had the highest share of all deaths in each use category: the percentage of deaths due to COPD was 59.7% during current use, 51.1% for recent use, 60.3% for past use, and 49.8% for never use (Table 15). 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. As in the 3 other countries, the adjusted HRs showed a clear trend with the highest HR in the lowest quintile and lowest HR in the highest PS quintile in NOR. The adjusted HRs in the fifth PS quintile was 0.79 (95% CI: 0.67, 0.93) (Table 25).

In the HDPS-matched patients, the adjusted 5-year all-cause mortality HR was 0.99 (95% CI: 0.91, 1.08) and did not indicate an increased risk for ever vs. never use (Table 38).

The secondary outcomes results (Table 26) were in general in line with the results for the other countries. An elevated risk of hospitalisations for respiratory diseases was observed for current use of roflumilast compared to never use, with adjusted HRs of 1.27 (95% CI: 1.17, 1.37) in SWE as seen in the other countries. An elevated risk of hospitalisations for respiratory diseases was also observed in association with recent and past use of roflumilast. 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 the risk estimate was lower than for respiratory disease-related hospitalisations with adjusted HR of 1.14 (95% CI: 1.06, 1.22) in NOR.

For hospitalisations due to diarrhoea of non-infectious origin for current use, the adjusted HR was elevated in NOR (HR: 2.03; 95% CI: 1.12, 3.67) as it was in SWE (HR: 1.55; 95% CI: 1.08, 2.24). The precision of the adjusted HR estimates was low for abnormal and unexplained weight loss and new diagnosis of depression due to the small number of events. The adjusted HR was 1.64 (95% CI: 0.80, 3.37) for abnormal and unexplained weight loss and 1.53 (95% CI: 0.43, 5.40) for new diagnosis of depression. These findings are in line with evidence described in the Final CSR for the other countries 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 available in NOR, as it was in SWE while in GER and the US, identification of new malignancies was based on claims data only and possibly resulted in under-ascertainment of malignancies. In NOR in the unexposed, crude IRs of malignant neoplasms (per 1000) were 328.40 (307.28, 350.98) (Table 17). In NOR, no elevated risk estimate was seen for no latency period (HR of 1.06 [95% CI: 0.91, 1.23]), latency period of 1 year (HR of 0.96 [95% CI: 0.81, 1.15]), and latency period of 2 years (HR of 1.04 [0.85, 1.27]) (Table 28). Analyses for solid tumours showed no clear differences for diverse latency allowance in NOR (Table 29). The adjusted HR was 0.94 (95% CI: 0.80, 1.09) in NOR when no latency was accounted for and did not diverge substantially with 1 or 2 years of latency. Reduced HRs were observed for the subgroups of haematopoietic cancers for ever-versus-never use of roflumilast; however, numbers of these cancers were very limited. Similarly, in SWE, 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 as reported in the Final CSR.

The meta-analysis showed substantial between-country heterogeneity for the primary study outcome, with increased HRs for 5-year mortality in two countries (GER and the US) and no increased risk in NOR and 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

Limitations of the study are discussed in the Final CSR. In addition, the NOR results are limited by the small sample size, which makes their interpretation more difficult.

11.3 Interpretation

Limitations of the study are discussed in the Final CSR.

11.4 Generalisability

Limitations of the study are discussed in the Final CSR.

12. OTHER INFORMATION (NOT APPLICABLE)

13. CONCLUSION

The results for the primary outcome in the main analysis for NOR were consistent with the results for SWE. In the comparison of ever use of roflumilast versus never use, no increased risk in mortality was observed in SWE and NOR while some increase in risk was seen in GER and the US as presented in the Final CSR. In the sensitivity analysis for the primary outcome where exposure was explored using exposure status at event (current, recent, and past), the NOR results were similar to SWE, GER, and the US where no increased risk was observed in current roflumilast users and a less than 1.5-fold increase in risk was observed for the recent and past use categories. In further sensitivity analysis, investigating cumulative exposure time (0 to 3 months, 3 to 12 months, 12 to 24 months, and > 24 months) results in NOR were similar to SWE, with no increase in mortality observed (as opposed to in GER and the US, where increased risks were generally observed). Finally, in the sensitivity analysis censoring patients at first discontinuation, results in NOR were similar to those in SWE and the US with no increase in risk observed.

Consistent with what was observed in GER, SWE, and the US, descriptive and analytical findings in NOR 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. The results of the HDPS for NOR were similar to the results from the analyses using conventional PS matching; hence this methodology may have been insufficient to completely eliminate the presence of residual and unmeasured confounders.

As was observed with GER, US, and SWE, a statistically significant increased risk was observed for respiratory disease-related hospitalisations, and all-cause hospitalisation that is

likely due to confounding by indication, informative censoring/selection bias over time, and important missing variables such as forced expiratory volume in 1 second and smoking. There was also a statistically significant increased risk observed for hospitalisation due to diarrhoea, a known side effect of roflumilast. However, no new risks compared with those that already emerged in the clinical development programme were observed. The risk of cancer was not significantly elevated for any latency category in NOR; this agrees with the outcome in SWE. In NOR as well as SWE, data were derived from a cancer registry with better data quality (in comparison to GER and the US which are based on claims data).

A meta-analysis was conducted for 5-year all-cause mortality for all 4 countries where the study was conducted. Results of the meta-analysis of all 4 countries showed substantial between-country heterogeneity with generally increased risks in 2 countries (GER and the US), and largely no elevated risks in SWE and NOR. In contrast to GER and the US, in NOR and SWE the variable “duration of COPD” was included in the PS model. Since “duration of COPD” is an important marker of COPD severity, inclusion of this variable into the PS model presumably gave a better balance between the exposed and unexposed cohort with respect to COPD severity, which might explain the discrepancies in the results between NOR and SWE compared to GER and US.

14. REFERENCES

Quan 2005
Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130-9.

15. TABLES NOT INCLUDED IN THE TEXT

Table 41 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 Norway

All-cause mortality	Norway	
	Never (reference)	Ever
Excluding patients who died within the first 3 months		
Deaths (PY)	2,853 (25,463)	731 (5,641)
N at risk	7,302	1,576
Crude HR (95% CI)	1 (reference)	1.09 (1.01, 1.18)
Adjusted HR[a] (95% CI)	1 (reference)	1.02 (0.94, 1.11)
Excluding patients who died within the first 12 months		
Deaths (PY)	1,996 (18,614)	582 (4,503)
N at risk	5,982	1,426
Crude HR (95% CI)	1 (reference)	1.13 (1.03, 1.24)
Adjusted[a] HR (95% CI)	1 (reference)	1.04 (0.94, 1.15)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 58

Table 42 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 in Norway

All-cause mortality		With 100% roflumilast gap extension			Without roflumilast gap extension		
	Never (reference)	Current	Recent	Past	Current	Recent	Past
Deaths (PY)	3251 (28036)	220 (2418)	66 (293)	493 (3327)	277 (2767)	44 (200)	458 (3070)
N at risk	7830	1624	1460	1195	1624	1181	1101
Crude HR (95% CI)	1.00 (Reference)	0.77 (0.68, 0.88)	1.78 (1.32, 2.41)	1.30 (1.17, 1.43)	0.71 (0.62, 0.81)	1.68 (1.31, 2.16)	1.28 (1.16, 1.41)
Adjusted[a] HR (95% CI)	1.00 (Reference)	0.78 (0.68, 0.88)	1.66 (1.22, 2.24)	1.14 (1.03, 1.27)	0.71 (0.62, 0.82)	1.61 (1.25, 2.06)	1.14 (1.03, 1.25)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 43

Table 43 5-Year All-cause Mortality Associated with Number of Roflumilast Dispensations Versus Never Use in Norway

All-cause mortality	Number of dispensations				
	Never (reference)	1	2-3	4-9	≥ 10
Deaths (PY)	3251 (28036)	293 (1879)	194 (1137)	139 (781)	153 (2238)
N at risk	7830	547	340	234	503
Crude HR (95% CI)	1.00 (Reference)	1.34 (1.19, 1.51)	1.39 (1.21, 1.61)	1.44 (1.21, 1.70)	0.54 (0.46, 0.64)
Adjusted[a] HR (95% CI)	1.00 (Reference)	1.15 (1.01, 1.29)	1.26 (1.09, 1.46)	1.41 (1.18, 1.67)	0.56 (0.47, 0.66)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 47

Table 44 5-year All-cause Mortality According to Ever-Versus-Never Use of Roflumilast for Patients With and Without Asthma in Norway

All-cause mortality	With asthma	Without asthma
Deaths (PY)	81 (907)	645 (4651)
N at risk	225	1275
Crude HR (95% CI)	1.11 (0.83, 1.48)	1.03 (0.94, 1.12)
Adjusted [a] HR (95% CI)	1.14 (0.83, 1.56)	0.96 (0.88, 1.06)

[a] Adjusted for age + sex + country-specific variables imbalanced after PS-matching (Table 9) + markers of COPD severity and morbidity (Final CSR 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; CSR = clinical study report; HR = hazard ratio; N = number of patients; PS = propensity score; PY = person-years.

Sources: Appendix 2 Table 48

APPENDICES