*In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.*

*The following guiding principles have been applied to the disclosure:*

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

# TITLE PAGE

**Division:** Worldwide Development

**Information Type:** Epidemiology PASS Final Study Report

| | |
|---|---|
| **Title:** | Post-authorization Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium (Study 201038) |
| **Phase:** | IV |
| **Compound Number:** | GSK2592356 (GSK573719+GW642444), GSK573719 |
| **Effective Date:** | 16 December 2023 |
| **Description:** | This is the final report of a PAS study fulfilling a commitment made in the European Union – Risk Management Plan (EU-RMP) for UMEC and UMEC/VI to examine the cardiovascular safety of these medications versus Tiotropium (TIO) in a real-world, post-approval setting |

**Subject:** Post-authorization Safety Study, Chronic Obstructive Pulmonary Disease (COPD), treatment, Cardiovascular diseases, Cerebrovascular diseases, Longitudinal Cohort, umeclidinium, vilanterol, tiotropium

**Author(s):** PPD

**Indication Studied: COPD**

## PASS INFORMATION

| | |
|---|---|
| **Title** | Post-authorization Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium (Study 201038). |
| **Version identifier of the final study report** | Version 1.0 |
| **Date of last version of the final study report** | Date: 16 December 2023 |
| **EU PAS register number** | EUPAS10316 |
| **Active substance** | Umeclidinium bromide (UMEC) and vilanterol trifenatate (VI) [ATC code: R03AL03], tiotropium bromide [ATC code: R03BB04] |
| **Medicinal product** | UMEC (INCRUSE ELLIPTA™, ROLUFTA ELLIPTA™), UMEC/VI (ANORO ELLIPTA™, LAVENTAIR ELLIPTA™) |
| **Product reference** | GSK573719 (UMEC)<br><br>GSK2592356 [GSK573719/GW642444] (UMEC/VI) |
| **Procedure number** | INCRUSE ELLIPTA/ROLUFTA ELLIPTA: EMEA/H/C/002809, EMEA/H/C/004654 ANORO ELLIPTA /LAVENTAIR ELLIPTA: EMEA/H/C/002751 EMEA/H/C/003754 |
| **Marketing authorization holder(s)** | GlaxoSmithKline (Ireland) Limited, GlaxoSmithKline Trading Services Limited |
| **Joint PASS** | Yes |
| **Research question and objectives** | The study addressed whether cardiovascular (CV) and cerebrovascular events differ for new users of umeclidinium bromide/vilanterol trifenatate (UMEC/VI) combination or umeclidinium bromide (UMEC) compared with new users of tiotropium (TIO) in participants diagnosed with chronic obstructive pulmonary disease (COPD). |

| | |
|---|---|
| | For new users of UMEC/VI combination, UMEC, or TIO, the primary objectives were:<br>• To demonstrate non-inferiority of UMEC/VI combination and UMEC to TIO for risk of the composite endpoint of myocardial infarction (MI), stroke, heart failure or sudden cardiac death based on an analysis of time to first event<br>• To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death<br>For new users of UMEC/VI combination, UMEC or TIO, the secondary objectives were:<br>• To compare UMEC/VI combination and UMEC to TIO for risk of MI, stroke and heart failure individually based on an analysis of time to first event<br>• To quantify the incidence rate and frequency of each of MI, stroke, and heart failure<br>• To quantify the incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)<br>• To quantify the overall mortality rate, cardiovascular and non-cardiovascular mortality rates<br>Details on other objectives (safety and effectiveness) are provided in Section 7. |
| **Countries of study** | Belgium, Czech Republic, Germany, Hungary, Italy, Netherlands, Poland, Spain, United Kingdom, United States |
| **Author** | PPD , Epidemiology Study Lead, Value Evidence and Outcomes, Global Research & Development, GlaxoSmithKline |

## MARKETING AUTHORIZATION HOLDER(S)

| | |
|---|---|
| Marketing authorization holder(s) | GlaxoSmithKline (Ireland) Limited<br>12 Riverwalk<br>Citywest Business Campus<br>Dublin 24<br>IRELAND<br><br>GlaxoSmithKline Trading Services Limited<br>12 Riverwalk<br>Citywest Business Campus<br>Dublin 24<br>D24 YK11<br>Ireland |
| MAH contact person | PPD, Team Lead Established products, Global Regulatory Affairs, GlaxoSmithKline Research & Development Limited |

**Table of Contents**

CCI [redacted]

# 1. ABSTRACT

## Title

Post-authorization Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium (Study 201038)

**Date of abstract:** 16 December 2023

**Main author:** PPD , PharmD, MPH, PhD
Epidemiology Study Lead, Value Evidence and Outcomes, Global R&D
GlaxoSmithKline

## Keywords

Post-authorization Safety Study, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases, umeclidinium, vilanterol, tiotropium

## Rationale and background

This post-authorization safety study (PASS) aimed to expand understanding of the potential cardiovascular (CV) and cerebrovascular risks of myocardial infarction (MI), stroke and new onset or acute worsening/decompensation heart failure of umeclidinium bromide/vilanterol trifenatate (UMEC/VI) or umeclidinium (UMEC) and compare them to tiotropium (TIO) for the treatment of chronic obstructive pulmonary disease (COPD).

## Research questions and objectives

Primary objectives (for new users of UMEC/VI combination, UMEC or TIO):

1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to TIO for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event
2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death

Secondary objectives (for new users of UMEC/VI combination, UMEC or TIO):

1. To compare UMEC/VI combination and UMEC to TIO for risk of MI, stroke and heart failure individually based on an analysis of time to first event
2. To quantify the incidence rate and frequency of each of MI, stroke, and heart failure
3. To quantify the incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)
4. To quantify the overall mortality rate, CV and non-CV mortality rates

Other objectives:

Safety (for new users of UMEC/VI combination, UMEC or TIO)

1. To quantify the incidence rate and frequency of hemorrhagic stroke, ischemic stroke, and undefined stroke
2. To quantify the incidence rate and frequency of hospitalization for heart failure
3. To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs)
4. To quantify the incidence rate and frequency of serious CV adverse events of special interest (CV AESIs), including transient ischemic attacks (TIAs) and angina pectoris, cardiac arrhythmias (including Torsades de pointes), acquired long QT interval, heart failure, cardiac ischemia, and hypertension

Effectiveness (for new users of UMEC/VI combination, UMEC or TIO)

1. To quantify persistence with study medication
2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalization)
3. To quantify all-cause and COPD-related health care utilization

## Study design

This was a multinational, prospective, observational, cohort study of COPD patients observed over at least a 24-month period. The index date was the initiation of UMEC/VI, UMEC, or TIO. The follow-up was the period between the index date until withdrawal of consent, loss to follow-up, the required number of adjudicated events were reached, or death.

## Setting

Participants were enrolled by primary care physicians and pulmonologists from 9 European countries and the US. Decisions regarding treatment were made at the sole discretion of the treating physician in accordance with their usual practices and independent from study participation.

## Subjects and study size, including dropouts

### Population

This study included participants aged 18 years and over with a clinical diagnosis of COPD that initiated one of the study medications (UMEC/VI, UMEC, or TIO) and with available medical records.

The estimated required number of events were intended to provide adequate power to demonstrate non-inferiority of UMEC/VI or UMEC relative to TIO, for the risk of the primary endpoint based on an analysis of time to first event. An estimated sample size of approximately 2233 participants per treatment cohort was required for the primary

endpoint analysis yielding a total required sample size of approximately 6700 total evaluable participants.

## Variables and data sources

Study variables included:

- The exposure variable based on the study treatment (UMEC, UMEC/VI, or TIO).
- Baseline variables such as demographics, disease burden, co-morbidities, prior and concomitant medication use, and patient-reported outcomes which were recorded at the enrollment visit.
- Safety outcomes included MI, strokes, heart failure, sudden cardiac death, serious pneumonia/serious LRTI events, mortality, SAEs, all serious CV AESI and all drug-related AEs, were captured at routine and unscheduled visits by their health care provider during the study follow-up period.
- Effectiveness outcomes included persistence with medication, moderate or severe COPD exacerbations, and health care utilization (all-cause and COPD-related).

**Data sources**

All data elements were collected from information routinely recorded in the medical record, or through participant self-report captured at routine and unscheduled visits. Hospital discharge summaries were requested by the investigator or site staff for all hospitalizations of enrolled participants. Data from these were captured in the electronic case report form (eCRF) and used for adjudication of CV and cerebrovascular events.

**Data analysis**

Demographic and clinical characteristics of each treatment cohort at the time of enrollment were summarized. For each characteristic, the standardized differences between those exposed to UMEC versus TIO or those exposed to UMEC/VI versus TIO were provided. Frequency, incidence rates, and event rates were computed for each treatment.

Propensity scores (PS) were used to ensure treatment cohorts were balanced and estimated separately for each treatment comparison.

For the main analysis, only events during the follow-up period which were confirmed upon adjudication were included. The number and percentage of participants experiencing each event and the incidence and event rate were summarized in the full analysis set (FAS) and the propensity scores matched (PSM) cohorts. Cox regression analyses were used to compare the time to first composite event from start of initiated treatment between UMEC and TIO cohorts, and UMEC/VI and TIO cohorts using stabilized inverse probability of treatment weighting (IPTW). The hazard ratio (HR) along with 95% confidence interval (CI) were calculated for each treatment comparison. If the upper bound of the 95% CI for the HR exceeded 2.0, the non-inferiority assumption was rejected. If the lower bound of the 95% CI was above 1.0, non-inferiority was not assumed.

Sensitivity analyses for the event rates and incidence rates for confirmed composite events were conducted using the full observation period. In addition, sensitivity analyses were

performed for primary outcomes focusing on the appropriateness of the IPTW method for adjusting for bias, including traditional multivariate analysis using covariate adjustment and PSM.

## Results

Out of 6606 participants enrolled in the study, 6165 were included in the FAS: 1246 (20.2%) participants were in the UMEC cohort, 2448 (39.7%) participants were in the UMEC/VI cohort, and 2471 (40.1%) were in the TIO cohort. The UMEC and TIO PSM cohorts included 1114 participants per treatment arm, and the UMEC/VI and TIO PSM cohorts included 1404 participants per treatment arm.

Primary outcomes

UMEC and UMEC/VI both demonstrated non-inferiority to TIO. The adjusted HR (95% CI) for the composite outcome was 1.254 (0.830, 1.896) for UMEC vs. TIO cohorts, and 1.352 (0.952, 1.922) for UMEC/VI vs. TIO.

Low rates of the composite events were observed across all cohorts. The frequency and corresponding incidence rates (95% CI) were 37 (1.157 [0.814, 1.594] per 100 person-years), 89 (1.287 [1.034, 1.584] per 100 person-years), and 67 (0.924 [0.716, 1.174] per 100 person-years) events among the UMEC, UMEC/VI, and TIO cohorts, respectively.

Secondary outcomes

Incidence rates of the composite endpoint components MI, stroke and heart failure ranged between 0.21 and 0.37 per 100 person-years across cohorts. The adjusted HR (95% CI) for MI was 1.754 (0.748, 4.115) for the UMEC vs TIO cohort and 2.195 (1.053, 4.575) for the UMEC/VI vs TIO cohort. The adjusted HR (95% CI) for stroke was 1.096 (0.458, 2.621) for the UMEC vs TIO cohort and 1.018 (0.470, 2.207) for the UMEC/VI vs TIO cohort. The adjusted HR (95% CI) for heart failure was 1.287 (0.654, 2.532) for the UMEC vs TIO and 0.832 (0.459, 1.509) for the UMEC/VI vs TIO cohorts.

Serious pneumonia/serious LRTI events were uncommon (approximately 3% of participants) in the UMEC and TIO PSM cohorts (37 and 34 participants with at least 1 event, respectively; incidence rate [95% CI]: 1.29 [0.906, 1.773] vs 1.05 [0.725, 1.462] per 100 person-years, respectively]). However, incidences of such events were higher in UMEC/VI vs TIO PSM cohort (72 vs 44 (1.79 vs 1.10 per 100 person-years).

The overall mortality rates (95% CI) during the observation period were 1.845 (1.468, 2.291), 2.561 (2.229, 2.928), and 1.912 (1.633, 2.225) deaths per 100 person-years for the UMEC, UMEC/VI, and TIO cohorts, respectively. The CV-related mortality rates (95% CI) for the observation period were 0.540 (0.346, 0.804), 1.065 (0.855, 1.311), and 0.664 (0.504, 0.859) per 100 person-years for the UMEC, UMEC/VI, and TIO cohorts, respectively. Lastly, the non-CV-related mortality rates (95% CI) were 1.305 (0.991, 1.687), 1.496 (1.245, 1.782), and 1.248 (1.025, 1.506) per 100 person-years for UMEC, UMEC/VI, and TIO cohorts, respectively.

Safety outcomes

For the UMEC vs TIO analysis, the total number of participants with at least 1 stroke (any type) and the corresponding incidence rates (95% CI) were 7 (0.24 [0.097, 0.495] 100 person-years) in the UMEC PSM cohort, and 7 (0.21 [0.086, 0.439] per 100 person-years) in the TIO PSM cohort. For the UMEC/VI vs TIO analysis, the total number of participants with at least 1 stroke (any type) and the corresponding incidence rates (95% CI) were 10 (0.24 [0.117, 0.448] per 100 person-years) and 12 (0.30 [0.153, 0.517] per 100 person-years).

Hospitalization for heart failure was uncommon in the study population and occurred in ≤2.0% of participants across all cohorts.

The incidence rate (95% CI) of SAEs was highest in the UMEC/VI cohort at 10.05 (9.266, 10.879) events per 100 person-years, followed by the UMEC cohort at 9.05 (7.973, 10.236) events per 100 person-years, then the TIO cohort at 7.61 (6.961, 8.313) events per 100 person-years. The incidence rate (95% CI) for drug-related AEs was highest in the UMEC cohort at 2.07 (1.569, 2.672) events per 100 person-years, followed by the UMEC/VI cohort at 1.40 (1.120, 1.734) events per 100 person-years, then the TIO cohort at 0.95 (0.725, 1.213) events per 100 person-years.

The incidence rate (95% CI) of serious cardiovascular or cerebrovascular AESIs was highest in the UMEC/VI cohort at 4.75 (4.219, 5.334) events per 100 person-years, followed by the UMEC cohort at 4.70 (3.936, 5.578) events per 100 person-years, and then the TIO cohort at 3.82 (3.357, 4.319) events per 100 person-years.

Effectiveness outcomes

A larger proportion of participants discontinued or switched their study drug in the UMEC cohort compared to the TIO cohort while UMEC/VI and TIO cohorts observed similar results. Adherence with study medication (medication possession ratio of ≥80%) demonstrated a similar pattern.

The incidence rate (95% CI) of moderate/severe COPD exacerbation was lowest among participants in the UMEC/VI cohort (7.42 [6.753, 8.137] per 100 person-years), slightly higher in the TIO cohort (8.83 [8.101, 9.607] per 100 person-years), and highest in the UMEC cohort (9.56 [8.445, 10.790] per 100 person-years).

In the UMEC and TIO PSM cohorts, healthcare provider (HCP) visit rates were similar at approximately 355 visits per 100 person-years, respectively. The UMEC PSM cohort had higher hospitalization rates compared to the TIO PSM cohort (UMEC: 14.92 hospitalizations per 100 person-years; TIO: 12.30 hospitalizations per 100 person-years). Emergency department (ED) visit rates were lower in the UMEC PSM cohort compared to the TIO PSM cohort (UMEC: 13.14 ED visits per 100 person-years; TIO: 15.34 ED visits per 100 person-years). HCP visit rates were lower in the UMEC/VI PSM cohort compared to the TIO PSM cohort (UMEC/VI: 269.08 visits per 100 person-years; TIO: 282.14 visits per 100 person-years). Hospitalization rates were higher in the UMEC/VI PSM cohort compared to the TIO PSM cohort (UMEC/VI: 12.27 hospitalizations per 100 person-years;

TIO: 10.14 hospitalizations per 100 person-years). ED visit rates were similar between the cohorts at approximately 10.5 visits per 100 person-years.

## Discussion

The study findings presented in this report support the conclusion that UMEC and UMEC/VI are both not inferior to TIO with regards to the risk of the composite endpoint (MI, stroke, heart failure, or sudden cardiac death). The number of cases and incidence rates for the composite and for each individual endpoint were notably low across all study cohorts.

There was no difference in risk of moderate/severe COPD exacerbation across cohorts (7.42-9.56 exacerbations per 100 person-years), consistent with previous observations. Although higher incidence rates of certain SAEs and drug-related AEs were observed in the UMEC and UMEC/VI cohorts compared to the TIO cohort, the differences were very small. The overall benefit/risk profile for both medications remain unchanged.

The study addressed the knowledge gap of the long-term safety risk profile of new users of UMEC and UMEC/VI compared to TIO. Results in this study provided valuable insights into the real-world safety and effectiveness for new users of UMEC and UMEC/VI compared to TIO. The study demonstrated no change in the benefit or the risk status for prescribing bronchodilators as treatment for patients with COPD.

## Marketing Authorization Holder

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
IRELAND

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
D24 YK11
Ireland

## Names and affiliations of principal investigator

Not applicable. There is no coordinating principal investigator at study-level for this study.

## 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AF | Atrial Fibrillation |
| AMI | Acute myocardial infarction |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CABG | Coronary Artery Bypass Grafting |
| CAP | Community-acquired pneumonia |
| CAT | COPD Assessment Test |
| CEVA | Clinical Event Validation and Adjudication |
| CI | Confidence Interval |
| CKD | Chronic Kidney Disease |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID | Coronavirus Disease |
| CRF | Case report form |
| CV | Cardiovascular |
| EAC | Event Adjudication Committee |
| EAS | Electronic adjudication system |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ED | Emergency department |
| EDC | Electronic Data Capture |
| FAS | Full Analysis Set |

| | |
|---|---|
| $FEV_1$ | Forced Expiratory Volume in one Second |
| FVC | Forced Vital Capacity |
| LBBB | Left bundle branch block |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| GSK | GlaxoSmithKline |
| HCP | Healthcare Provider |
| HR | Hazard ratio |
| HDL | High density lipoprotein |
| ICF | Informed Consent Form |
| ICS | Inhaled Corticosteroids |
| IPTW | Inverse Probability of Treatment Weighting |
| LABA | Long-acting beta2-agonist |
| LAMA | Long-acting Muscarinic Antagonist |
| LDL | Low density lipoprotein |
| LRTI | Lower Respiratory Tract Infection |
| LTOT | Long-term Oxygen Therapy |
| MACE | Major adverse cardiovascular events |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| mMRC | Modified Medical Research Council |
| MPR | Medication Possession Ratio |
| NYHA | New York Heart Association |
| PAS | Post-Authorization Safety |
| PASS | Post-Authorization Safety Study |

| | |
|---|---|
| PCI | Percutaneous Coronary Intervention |
| PDC | Proportion Of Days Covered |
| PI | Principal Investigator |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PRO | Patient-reported Outcome |
| PS | Propensity scores |
| PSM | Propensity Score Matched |
| PT | Preferred Term |
| RCT | Randomized Controlled Trial |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SD | Standard Deviation |
| SM | Site Manager |
| SOC | System Organ Class |
| SSC | Scientific Steering Committee |
| Std Diff | Standardized Difference |
| TIA | Transient Ischemic Attack |
| TIO | Tiotropium |
| UMEC | Umeclidinium bromide |
| UMEC/VI | Umeclidinium bromide/vilanterol trifenatate |
| UPLIFT | Understanding Potential Long-Term Impacts on Function with Tiotropium |
| US | United States |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| ANORO ELLIPTA |
| INCRUSE ELLIPTA |
| LAVENTAIR ELLIPTA |
| ROLUFTA ELLIPTA |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| Braltus |
| Spiriva Respimat |
| Spiriva Handihaler |
| Tutast Sanohaler |

# 3. INVESTIGATORS

There was no principal nor coordinating investigator assigned to the study. The list of all site-level investigators including contact details are kept in a stand-alone document in ANNEX 1- List of investigators.

# 4. OTHER RESPONSIBLE PARTIES

## Sponsor

The Marketing Authorization Holder (MAH), GSK serves as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

## Study Coordination

The MAH, GSK contracted CCI, a contract research organization specialized in registries and observational post-market studies, to support and to conduct the study in line with ICH GCP rules with review and input from GSK.

## Sponsor signatory

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study 201038.

| | |
|---|---|
| Peter Zammit-Tabona<br>Study Accountable Person | **Date** |

| | |
|---|---|
| David Slade<br>Therapy Area Leader/+1 Manager | **Date** |

| | |
|---|---|
| Paweł Kapuściński<br>Head, Safety Evaluation and Risk Management | **Date** |

## Scientific Steering Committee

The composition of the Scientific Steering Committee (SSC) was 5 external members with relevant clinical and epidemiologic experience, as well as GSK employees (epidemiology lead, clinical science lead, medical lead, stats lead, and operations lead), and one representative from CCI [redacted]. Details on the SSC are described in the SSC charter kept in a stand-alone document (listed in ANNEX 1- Charter of Scientific steering committee) and is available upon request.

The SSC provided expert medical and epidemiological input and advice, review of the interim and final reports of safety data and monitors the overall study progress through regular teleconferences and meetings.

**External members were:**

Chairperson PPD . All members have experience and expertise in their field of practice.

**Current GSK members were:**

PPD .

If requested by an SSC member, additional representatives from GSK may be present at meetings in an advisory capacity, to address SSC questions and to be a resource if the SSC requested additional data or follow-up information. These included but were not limited to: PPD .

The CCI steering committee coordinator was PPD .

SSC Chairperson and members were selected based on their experience in their field of expertise. The SSC Chair was chosen based on epidemiology and biostatistics experience as well as experience in clinical pharmacology and respiratory medicine. The SSC membership included therapeutic experts in respiratory medicine, clinical pharmacology, cardiology, epidemiology, clinical trials and statistical methods. SSC members were approved by the GSK Medicine Development Lead. In the event that a member was unable to continue participation on the SSC, the SSC Chair agreed on a replacement. GSK had the final decision as to the replacement. No substitution of members, either by the Chair or other members, was permissible for meetings.

The SSC worked with the Sponsor (GSK) to ensure proper study conduct and conformance with the protocol:

1. Provided input into study design, outcomes definition and protocol development.
2. Reviewed the study protocol and any amendments.
3. Provided expert support in dialogue with the Pharmacovigilance Risk Assessment Committee (PRAC).
4. Reviewed study progress and advised on any clinical or methodological issues emerging during the study.
5. Reviewed the draft SSC Charter and made recommendations for change(s).
6. Reviewed summarized safety and efficacy data for risk/benefit information.
7. Advised and agreed on the data analysis and interpretation of the results of the study.
8. Provided input to GSK's Safety Review Team with respect to any emergent/unexpected safety issues arising during the course of the study.
9. Advised on study-related publications and presentation plans.
10. Authored and presented study-related publications and presentations at external meetings.
11. SSC Chairperson chaired the SSC meetings.

### Event Adjudication Committee

An Event Adjudication Committee (EAC) adjudicated cardiovascular (CV) and cerebrovascular events of interest in a blinded fashion throughout the study. The EAC included 4 independent medical specialists in cardiology and one neurologist, who conducted a blinded review of relevant data and documentation and validated events as confirmed or unconfirmed based on predefined algorithms.

## 5. MILESTONES

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection | 2016 | 02 February 2016 | The first participant first visit (FPFV) occurred on 02 February 2016 |
| End of data collection | 31 March 2024 | 31 January 2023 | The last participant last visit (LPLV) occurred on 31 January 2023 |
| Registration in the EU PAS register | 17 July 2015 | 17 July 2015 | |
| Interim report 1 | 31 March 2021 | 12 March 2021 | 6 months post last participant first visit (LPFV) |
| Final report of study results | 30 September 2024 | 16 December 2023 | |

## 6. RATIONALE AND BACKGROUND

### 6.1. Background

As per Global Initiative for Chronic Obstructive Lung Disease (GOLD), chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms [Agustí, 2023a]. The resulting clinical manifestations include dyspnea, chronic cough/expectoration and/or exacerbations that could be due to airways abnormalities and/or abnormality of alveoli (emphysema) and lead to progressive, persistent airflow obstruction [Agustí, 2023a; GOLD 2024]. In 2019, COPD was the third leading cause of death globally, claiming the lives of 3.3 million people [WHO, 2020] and therefore demand for effective treatments has increased.

During the development of the study protocol, GOLD guidelines recommended spirometry analysis as the key for diagnosis of COPD; and a post-bronchodilator forced expiratory volume in one second/forced vital capacity ($FEV_1$/FVC ratio of <0.7) confirms persistent airflow limitation in a patient [GOLD 2017]. GOLD guidelines are revised annually to include the latest information available. These guidelines were updated during the conduct of this study which has a potential to impact clinical practice. The GOLD 2023

recommendations that were released in November 2022 guide healthcare providers to diagnose and begin treatments for COPD earlier than before [Tamondong-Lachica, 2023]. Overall, the diagnosis considerations used in this study are still relevant per the GOLD 2023 guidelines which supported the generalizability of the study results to current clinical practice [GOLD 2023].

Umeclidinium bromide/vilanterol trifenatate (UMEC/VI) (ANORO™/Laventair™) and umeclidinium bromide (UMEC) (INCRUSE™/ROLUFTA™) are 2 inhaled medications developed by GlaxoSmithKline (GSK) and serve as maintenance bronchodilator treatments indicated to relieve symptoms in adult patients with COPD. These were approved by the European Commission in 2014 (ROLUFTA in 2017). UMEC/VI is a fixed dose- combination long-acting muscarinic antagonist (LAMA)/ long-acting beta2-agonist (LABA) for the treatment of COPD. UMEC is a LAMA indicated for the maintenance treatment of COPD. Vilanterol (VI) is a LABA that is also part of a combination inhaled corticosteroid (ICS)/LABA with fluticasone furoate (RELVAR™) approved for the treatment of COPD.

Current GOLD guidelines recommend use of inhaled LAMAs and LABAs for maintenance treatment of COPD [GOLD 2024]. The combination of 2 classes of COPD therapies, each with a distinct mode of action, has been shown to be more effective at improving lung function and reducing symptoms [Donohue, 2013; Celli, 2014; Decramer, 2014] than either therapy alone. Compared with monotherapies, the combination (LABA+LAMA) has favorable improvements in the majority of outcomes irrespective of baseline health-related quality of life [Vogelmeier, 2020]. A systematic review of direct and indirect treatment comparisons assessing efficacy and safety of LAMA/LABA fixed-dose combination therapies in COPD patients concluded that combination has a comparable efficacy and safety in patients with COPD and moderate to very severe airflow limitations [Hurst, 2020].

The safety and efficacy of monocomponent LABA and LAMA containing medications in COPD have been studied extensively. LAMA containing medications are considered a gold standard of bronchodilation for COPD patients demonstrating benefits of improved lung function and dyspnea reduction. Both the LABA and LAMA class of drugs have been associated with some increased risk of cardiovascular (CV) and cerebrovascular events in meta-analyses of randomized clinical trials [Salpeter, 2004; Singh, 2011; Singh, 2013].

In a meta-analysis conducted by Singh et al., comprised of 17 trials enrolling 14,783 patients, the rate of CV and cerebrovascular events was increased by 58% among patients who used inhaled muscarinic antagonists for more than 30 days [Singh, 2008]. Increased risks of CV death, myocardial infarction (MI), and stroke were predominantly apparent in long-term trials. However, given that none of the included trials were designed a priori to monitor for CV risk, and that the trials were generally of short duration, failed to adjudicate outcome events, and were unable to control for strong confounders (e.g., smoking, hypertension, and diabetes), the results of this meta-analysis were inconclusive.

Tiotropium (TIO) is a LAMA which is well-established as a treatment for stable COPD. In a 4 -year randomized controlled trial (RCT) (Understanding Potential Long-Term Impacts on Function with Tiotropium [UPLIFT] study), published after the Singh et al. meta-analysis, investigators noted a decreased risk for fatal CV events in patients

randomized to TIO (rate ratio=0.57) [Tashkin, 2008]. Considering the contradictory evidence, Celli and colleagues conducted a meta-analysis that re-analyzed CV risk among COPD patients taking muscarinic antagonists compared to placebo [Celli, 2010]. Their findings (rate ratio=0.83) were consistent with results from the UPLIFT study, supporting the hypothesis that LAMAs are not an independent risk factor for CV death, MI or stroke. Another study reported no difference in the risk of CV events in TIO (commercially known as Handihaler) users versus users of other respiratory medications [deLuis, 2007]. Three studies explored the risk of CV and cerebrovascular events in TIO (Handihaler) users versus LABA users [Gershon, 2013; Jara, 2007; Jara, 2012]. Only the risk of stroke was significantly increased and only in one study among TIO users [Gershon, 2013]. This was not identified in the 2 other studies.

More recent clinical studies demonstrated that LAMA had greater effect on exacerbation rates compared with LABA [Decramer, 2013; Vogelmeier, 2011]. In studies with patient-reported outcomes (PROs) as primary endpoint, the combination therapy demonstrated higher impact on PROs compared with monotherapies [GOLD 2024]. A systematic review and meta-analysis assessing efficacy and cardiovascular safety of LAMA in patients with COPD demonstrated LAMA as a safe therapy that improves lung function and reduces exacerbations [Zhang, 2021]. Another systematic review that included 19 RCTs (conducted in 28211 stable COPD patients) demonstrated that treatment with LAMA had a significantly lower incidence of exacerbations and non-serious adverse events (AEs) along with higher trough $FEV_1$ compared to LABA [Koarai, 2020]. Similar results were concluded in a non-interventional database study assessing effectiveness and safety of COPD maintenance therapy with TIO/olodaterol versus LABA/ICS in a United States (US) claims database [Quint, 2021]. The study demonstrated reduced risk of COPD exacerbations irrespective of baseline eosinophils or exacerbation history.

Pooled analysis of 8 Phase 3 RCTs showed no clinically relevant increase in CV events with UMEC/VI or UMEC compared with placebo. The number of cardiac ischemic events was low and inconsistent with small imbalances between treatments observed in some individual studies. No increased risk of major CV events (adjudicated CV death, stroke or cardiac ischemia/MI) was observed with UMEC/VI or UMEC compared to placebo. A small increase in atrial arrhythmias was observed with UMEC compared to placebo which has been observed previously with other LAMAs [Naccarelli, 2014; Anthonisen, 2002].

Given the high prevalence of CV co-morbidities among COPD patients, observational research that aims to elucidate causal relationships between LAMAs and CV events is an important approach to monitor patient safety [Fabbri, 2008; Müllerova, 2013]. As such, this study collected data to increase understanding of the risk benefit profiles of UMEC/VI or UMEC, while examining the long-term safety risk profile of UMEC/VI and UMEC compared with new users of TIO in the real-world setting. Due to the infrequency of individual endpoints among patients with COPD, the study also aimed to investigate the incidence of a composite endpoint.

## 6.2. Rationale

GSK conducted this observational study to collect data reflecting the ‘real-world’ experience with UMEC/VI combination and UMEC in the post-approval setting to expand

the understanding of potential CV risks (MI, stroke, heart failure and sudden cardiac death) in COPD patients. This was a category 1 (imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization) study and was approved by PRAC and conducted as part of a post-marketing obligation by the European Commission.

This was an observational cohort study evaluating non-inferiority of the composite endpoint (MI, stroke, heart failure and sudden cardiac death) among COPD patients initiating treatment with UMEC/VI, UMEC or TIO. Due to the low rate of individual cardiovascular events observed at the beginning of the study, in 2020 the primary endpoint changed from individual events to composite events (see Section 8).

# 7. RESEARCH QUESTION AND OBJECTIVES

The study addressed whether the incidence rates of CV and cerebrovascular events differed for new users of UMEC/VI combination or UMEC compared with TIO in participants diagnosed with COPD.

Primary objectives (for new users of UMEC/VI combination, UMEC or TIO)

1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to TIO for risk of the composite endpoint of MI, stroke, heart failure, or sudden cardiac death based on an analysis of time to first event
2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death

Secondary objectives (for new users of UMEC/VI combination, UMEC or TIO)

1. To compare UMEC/VI combination and UMEC to TIO for risk of MI, stroke, and heart failure individually based on an analysis of time to first event
2. To quantify the incidence rate and frequency of each of MI, stroke, and heart failure
3. To quantify the incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)
4. To quantify the overall mortality rate, CV, and non-CV mortality rates

Other objectives

*Safety (for new users of UMEC/VI combination, UMEC or TIO)*

1. To quantify the incidence rate and frequency of hemorrhagic stroke, ischemic stroke and undefined stroke
2. To quantify the incidence rate and frequency of hospitalization for heart failure
3. To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related AEs
4. To quantify the incidence rate and frequency of serious CV events of special interest (CV AESIs), including transient ischemic attacks (TIAs) and angina pectoris, cardiac arrhythmias (including Torsades de pointes), acquired long QT interval, heart failure, cardiac ischemia, and hypertension

*Effectiveness (for new users of UMEC/VI combination, UMEC or TIO)*

1. To quantify persistence with study medication
2. To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalization)
3. To quantify all-cause and COPD-related health care utilization

## 8. AMENDMENTS AND UPDATES

The main amendment to the protocol was to have the composite endpoint as the primary endpoint due to infrequency of single endpoints and to evaluate non-inferiority of the composite endpoint. Only the original protocol _00 and the protocol version _04 were submitted to the ethics committees (see ANNEX 1 – Independent Ethics Committee-Institutional Review Board list).

| GSK Document Number | Date | Version | Amendments or Updates |
|---|---|---|---|
| 2014N206201_00 | 01 April 2015 | Original | Not applicable. |
| 2014N206201_01 | 13 July 2018 | Amendment No. 1 | Change in study objectives including removal of non-inferiority driven safety analysis. |
| 2014N206201_02 | 28 November 2018 | Amendment No. 2 | A comparative analysis will be performed among treatment groups and the sample size in this event driven study is based on a composite endpoint. |
| 2014N206201_03 | 02 May 2019 | Amendment No. 3 | The number of participants and the average duration of follow-up have been increased in order to achieve the number of events required for composite endpoint. The milestones have also been adjusted accordingly. |
| 2014N206201_04 | 25 July 2019 | Amendment No. 4 | Greater granularity was provided in the dates of the expected milestones and additional analysis |

| | | | |
|---|---|---|---|
| | | | was added for the composite endpoint to include stratification by exacerbation history. |

# 9. RESEARCH METHODS

## 9.1. Study design

This was a multinational, prospective, observational, nonrandomized study carried out in 9 European countries (Belgium, Czech Republic, Germany, Hungary, Italy, Netherlands, Poland, Spain, and the United Kingdom) and in the US having UMEC/VI, UMEC, and TIO available on prescription.

Participants were enrolled in the study at the time of a new UMEC/VI, UMEC, or TIO prescription. This was consistent with a new user design recommended for observational studies of medication effects to avoid bias associated with inclusion of prevalent users of a medication who "survived" and continued taking the drug beyond the period of early use [Ray, 2003].

Participants were observed individually over at least a 24-month time frame, or until withdrawal of consent, lost to follow-up, or death. During this period, data were collected at routine and unscheduled visits to the treating physician as they occurred. Routine visits were expected to be at least twice yearly as part of normal care. Participants who were not seen for a period of 6 months were contacted directly by their health care provider to collect minimal participant safety information, provided that this contact was considered by the treating physician to be within the standard of care for this participant. Hospital discharge summaries were also collected. Prior and concurrent CV or cerebrovascular disease history and history of pneumonia and LRTIs were recorded at enrollment as well as the modified Medical Research Council (mMRC) and COPD Assessment Test (CAT).

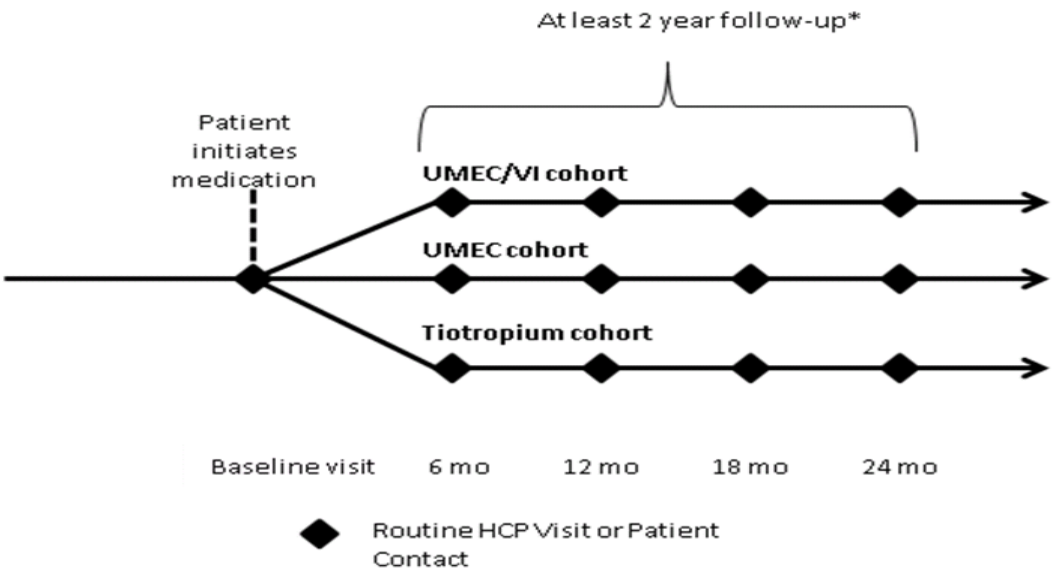
Participants who were enrolled in the study had a clinically valid diagnosis of COPD made in accordance with GOLD guidelines, and were only enrolled when a spirometric diagnosis of COPD was available. It is important to note that the GOLD guidelines changed throughout the duration of this study and so data from both guidelines were presented in this study. At no point were participants requested to undergo a spirometry procedure solely for the purposes of participating in this study. The decision to initiate use of UMEC/VI, UMEC, or TIO was made independently by the participant and their treating physician and was not mandated by the study design or protocol. Medication switches or the addition of other COPD medications could have occurred at any time point during the study at the discretion of the treating healthcare provider (HCP).

For the analyses of the primary outcome, participants were considered censored at 14 days after discontinuation of the initiated medication (UMEC/VI, UMEC, or TIO), at the end of the exposure period, withdrawal to the study, or death, whichever came first. The exposure period was defined as the period from the prescription index date to the date of discontinuation of the initial prescribed study medication plus 14 days, or to date of medication switch to another COPD medication whichever came first.

Participants were encouraged and expected to remain in the study until the conclusion of study follow-up regardless of discontinuation of the initiated study medication (UMEC/VI, UMEC, or TIO). The period from prescription index date to censoring (including consent withdrawal) or ≥24 months of follow-up regardless of discontinuation of the initiated study medication was defined as the observation period.

Figure 1 provides a schematic of the study design and follow-up schedule.

**Figure 1 Design and Follow-up Schedule for COPD PASS**




COPD: Chronic obstructive pulmonary disease; HCP: healthcare provider; mo: months;
PASS: Post-Authorization Safety Study; UMEC: Umeclidinium bromide; VI: Vilanterol trifenatate.
*The follow-up period was defined as the period between the prescription index date until the earliest of: 2 years after the date of the planned number of events reached, 14 days following date of discontinuation of index COPD medication (if this was the reason for study discontinuation), withdrawal from the study, conclusion of study follow-up, or death.

Details of expected contacts with the treating physician and scheduled assessments for the study are presented in Table 1 displayed in Section 9.5.

## 9.2. Setting

Eligible participants were enrolled by primary care physicians and pulmonologists from 358 centers throughout selected EU countries and the US. Enrollment in the US was capped at approximately 50%. Site selection criteria included experience in treating participants with COPD, ability to prescribe the 3 treatments (UMEC/VI, UMEC, or TIO), access to the eligible population, ability to comply with study protocol procedures, and adequate site resources to meet study requirements. Selection criteria and basic site information (e.g., site size, site type) were collected via a site qualification survey.

Sites were required to maintain a participant enrollment log of eligible participants at their treatment centers to document how participants were included or excluded from the study. The study did not provide or recommend any treatment. All decisions regarding treatment were made at the sole discretion of the treating physician in accordance with their usual practices. The decision to enroll a participant in this study was not made until after the treating physician had prescribed 1 of the 3 study treatments. All participants presenting at a given site during the enrollment period were assessed for eligibility according to the defined selection criteria, and all eligible participants at a site were to be consecutively enrolled in the study to the extent feasible. Frequent interim monitoring of participant recruitment into each of the 3 treatment cohorts at a site and country level was conducted so that recruitment could be adapted when needed. However, no adaptations were required for this study.

At least 98 participants with an adjudicated event for the composite endpoint (stroke, MI, heart failure, sudden cardiac death) for both planned exposure comparisons (UMEC vs TIO; UMEC/VI vs TIO), were obtained by the last participant last visit on 31 January 2023.

## 9.3. Subjects

### 9.3.1. Inclusion criteria

The following criteria had to be met for participant to be enrolled in the study:

- A clinical diagnosis of COPD verified by spirometry (defined as a post-bronchodilator forced expiratory volume in one second/forced vital capacity [$FEV_1$/FVC] ratio of <0.7). It is to be noted that at no point were any participants. Requested to have spirometry solely for the purposes of participating in this study
- Initiation of treatment with 1 of the 3 study treatments, UMEC/VI, UMEC, or TIO according to the decision of the treating physician (an index prescription could precede enrollment visit by up to 7 days)
- Adult over 18 years of age willing and able to provide written informed consent
- Participant with medical records available for at least the 12-month period prior to enrollment
- Participant able to read and write

### 9.3.2. Exclusion criteria

Participant meeting the following criteria were not eligible for participation:

- Current participation in any interventional clinical trials in which treatment regimen and/or monitoring was dictated by a protocol
- Participants with hypersensitivity to UMEC, VI, TIO, or excipients
- Maintenance treatment with a LAMA containing medication during the 12 months prior to enrollment. Maintenance treatment is defined as 60 or more days of continuous use.

### 9.3.3. Patient withdrawal

Participants could withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a participant withdrew prior to completing study follow-up period, any known reason for withdrawal had to be documented in the database. In cases where contact could not be made with the participant, the participant was considered lost to follow-up after the site attempted actions for contact. All information already collected as part of the study was retained for analysis; however, no further efforts were made to obtain or record additional information regarding the participant. Participants were encouraged and expected to remain in the study until the conclusion of study follow-up regardless of discontinuation of the initiated study medication (UMEC/VI, UMEC, or TIO).

### 9.3.4. Patient completion of the study

All participants were followed-up in the study for at least 2 years, if possible, until study withdrawal, death, or conclusion of study follow-up. Patients were defined as having completed the study if some follow-up safety data were collected with no study discontinuation, loss to follow-up or withdrawal of consent during the observation period or before site or study end. Death, exposure switch, augmentation, and/or exposure discontinuation were allowed, and the patient was still deemed to have completed the study.

## 9.4. Variables

### 9.4.1. Exposure definitions

This was an observational safety study of real-world treatment practice of new users of UMEC/VI, UMEC, or TIO for COPD. This study did not recommend the use of any specific treatments. No study medication was provided as part of participation.

As a long-term observational study to evaluate treatment patterns and outcomes in patients treated in the post-marketing setting, no restrictions on concomitant treatments were associated with the study. All concomitant treatments including concomitant use of ICS-containing medications were carefully recorded to evaluate their potential influence on the outcomes of interest.

Classification of exposure to UMEC/VI, UMEC, or TIO were based on the data obtained from the treating physician, participant medical charts, and participant self-report. The exposure information was therefore to be recorded before the occurrence of outcomes in this prospective study and confirmation of CV and cerebrovascular endpoints by the EAC were conducted blinded to exposure status.

Three new user cohorts were defined as follows:

1. New users of UMEC/VI
2. New users of UMEC
3. New users of TIO

For these 3 cohorts of new users all the following conditions were applied:

- New user was defined by the first prescription for this medication.
- The date of the first prescription was the study start date. This was also described as the prescription index date.
- No maintenance treatment with LAMA containing medication in the 12 months prior to enrollment. Maintenance treatment was defined as 60 or more days of continuous use.

Note: Reason for the choice of LAMA containing medication prior to initial prescription index date was rigorously recorded.

Participants were classified as exposed to UMEC/VI, UMEC, or TIO beginning on the date of first prescription (index date, which could be at enrollment visit or up to 7 days prior to the enrollment visit) and ending 14 days after the date of discontinuation. This was defined as the exposure period and add-on treatments were permitted during the whole study period.

### 9.4.2. Outcome definitions

The primary outcomes of this study were:

- Time to first event within the composite endpoint (MI or stroke, or new onset, or acute worsening/decompensation heart failure or sudden cardiac death)
- Incidence rate of composite endpoint of MI, stroke, or new onset, or acute worsening/decompensation heart failure or sudden cardiac death (number of first event per 100 person-years)

Definitions for the primary safety outcomes used as guidelines for event adjudication by the EAC are provided in ANNEX 1- Charter of the adjudication committee.

The secondary outcomes of this study were:

- Time to first MI
- Time to first stroke
- Time to first heart failure event (new onset, or acute worsening/decompensation)
- Incidence rate of MI (number of first events per person-year)
- Incidence rate of stroke (number of first events per person-year)
- Incidence rate of new onset, or acute worsening/decompensation heart failure (number of first events per person-year)
- Total number of events (including recurrent events) of each of MI, stroke, and new onset, or acute worsening/decompensation heart failure
- Incidence rate of serious pneumonia/ serious LRTI events (number of first event per person-year)
- Total number of events (including recurrent events) and event rate (total number of events per person-year) of all pneumonia/LRTI AEs
- Mortality rates (number of events per person-year) for all-cause mortality, CV mortality, and non-CV mortality
- Number and percentage of participants who died and the total number of deaths (all-cause, CV, and non-CV)

Treatment safety outcomes included:

- Incidence rate of hemorrhagic stroke, ischemic stroke, and undefined stroke (number of first event per person-year)
- Total number of events (including recurrent events) for both hemorrhagic stroke, ischemic stroke, and undefined stroke
- Incidence rate (number of first event per person-year) of hospitalization for heart failure
- Total number of events (including recurrent events) for hospitalization for heart failure
- Incidence rate (number of first events per person-year) of all reported SAEs, summarized according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT)
- Total number of events (including recurrent events) of all reported SAEs, summarized according to MedDRA SOC and PT
- Incidence rate (number of first events per person-year) of all reported drug-related AEs, summarized according to MedDRA SOC and PT
- Total number of events (including recurrent events) of all reported drug-related AEs, summarized according to MedDRA SOC and PT
- Incidence rate (number of first events per person-year) of all reported serious CV AESIs, including, but not limited to:
    - transient ischemic attacks
    - angina
    - cardiac arrhythmias
    - acquired long QT interval (including Torsades de Pointes)
    - cardiac ischemia
    - hypertension

Treatment effectiveness outcomes included:

- Persistence with initiated medication (including time from start date to date of discontinuation or switch in therapy, allowing for a defined "permissible gap" of ≤30 days in use; Medication Possession Ratio [MPR] and Proportion Days Covered [PDC])
- Time to (earliest of) discontinuation of initiated COPD medication (including death or withdrawal from the study) or change in COPD maintenance medication from start of initiated treatment
- Time to first moderate/severe COPD exacerbation (i.e., requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalization)
- Rate of moderate/severe COPD exacerbation per year (total number of events per person-year)
- Rate of hospitalizations per year from all causes (total number of events per person-year)
- Rate of COPD-related hospitalizations per year (total number of events per person-year)
- Rate of emergency department (ED) visits per year from all causes (total number of events per person-year)

- Rate of COPD-related ED visits (total number of events per person-year)
- Rate of health care utilization including visits to the treating physician, hospitalizations and ED visits from all causes (total number of events per person-year)
- Rate of COPD-related health care utilization including visits to the treating physician, hospitalizations and ED visits (total number of events per person-year)

### 9.4.3. Confounders and effect modifiers

Propensity scores (PS) were estimated for each pairwise treatment comparison using multivariable logistic regression models to compute a predicted probability of initiating either UMEC/VI or UMEC each compared with TIO. The set of covariates (and their first-order interactions) considered for inclusion in the stepwise logistic regression models for the PS model included the list of measures below, assessed at the time of study enrollment; variable selection was performed separately for each treatment comparison and was based on a priori clinical relevance and/or statistical significance within the multivariable model. The potential confounders and effect modifiers of primary outcomes included:

- Site characteristics:
  - Primary care or specialist (pulmonologist or other)
  - Care setting
- Participant demographics:
  - Country of enrollment
  - Date of enrollment
  - Age
  - Gender
  - Race and ethnicity
  - Highest educational level reached
  - Predominant occupation during working age, e.g., manual/clerical/management/homemaker
- Clinical assessments:
  - Body mass index (BMI)
  - Systolic and diastolic blood pressure (BP)
  - New York Heart Association (NYHA) heart failure class
  - Total cholesterol
  - Low density lipoprotein (LDL) cholesterol
  - High density lipoprotein (HDL) cholesterol
  - Triglycerides
  - Prior CVD-related hospitalizations (last 12 months)
- COPD severity:
  - Spirometric measures: $FEV_1$/FVC and $FEV_1$ % predicted
  - Age at COPD diagnosis
  - GOLD classification
  - Number of moderate/severe COPD exacerbations (past 12 months)
  - Number of COPD exacerbation-related hospitalization (past 12 months)
- Smoking and alcohol history:

  - Smoking status (current, ex-smoker, non-smoker)
  - Alcohol use (units/week)
- History of CV and cerebrovascular diagnosis:
  - MI
  - Number of MI events
  - Unstable angina requiring hospitalization
  - Number of angina events
  - TIA
  - Number of TIA, heart failure
  - Pathological brady arrhythmias
  - Tachycardia
  - Stroke (all types)
  - Number of stroke events
  - Hypertension
- History of other co-morbidities:
  - Asthma
  - Pneumonia/LRTI (past 12 months)
  - Diabetes
  - Glaucoma
  - Psychiatric disorders
  - Dyslipidemia
  - Chronic kidney disease (CKD)
  - Cancer (malignant/benign) including lung cancer
  - Dyslipidemia was also assessed by collecting the most recent information on total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides each as recorded in past 12 months. Psychiatric disorders and glaucoma were also assessed indirectly through the list of concomitant medications used to treat such conditions.
- Family history of CV and cerebrovascular diagnoses – first-degree relatives:
  - Male relative with CV events less than age 55 years
  - Female relative with CV events less than age 60 years
- Concomitant medications/therapies of interest including respiratory medications:
  - Non-COPD medications including lipid lowering agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists (ARBs), anti-anginals, anti-arrhythmics, anti-coagulants, anti-platelets, betablockers, calcium channel blockers, digitalis, diuretics, insulin, oral antidiabetics, systemic exposure to glucocorticosteroids, antidepressants, glaucoma medications, and cytostatics with CV damage potential

Information on all medications taken at study enrollment and during the prior 12 months were collected via electronic case report form (eCRF) and a binary indicator flag (Use: Yes/Non-use) derived. Based on this information, all therapeutic agents, through pharmacotherapeutic groups, that were potentially associated with the risk of the composite primary endpoint and exposure, or the primary outcomes only, were considered for inclusion in the propensity score and as covariates in multivariable models. Detailed information on prior exposure to COPD medications, in the 12 months prior to enrollment, was also collected and accounted for in the analysis in a similar fashion.

- Medications used to treat COPD including LAMA (other than TIO, UMEC), LAMA (TIO), LAMA (UMEC), LABA, LAMA+LABA (other than UMEC/VI), LAMA+LABA (UMEC/VI), ICS, ICS+LAMA, ICS +LABA, Oral corticosteroids, roflumilast, theophyllines, and other COPD medications
- Other treatments and medications:
    - Long-term oxygen therapy and influenza vaccination in previous 12 months
- PRO measures: mMRC dyspnea scale and CAT

## 9.5. Data sources and measurement

Scheduled assessments for the study are presented in Table 1. All data elements were prospectively collected via eCRF from information routinely recorded in the medical records, recorded by the investigator for the purposes of the study, or through participant self-report. Hospital discharge summaries were requested by the investigator or site staff for all hospitalizations among enrolled participants.

Information regarding the use of study medication and concomitant medication was captured at routine and unscheduled visits. Event information, including MI, stroke and new onset, or acute worsening/decompensation heart failure, sudden cardiac death, all serious pneumonia/serious LRTI, CV mortality and non-CV mortality, hemorrhagic stroke, ischemic stroke and undefined stroke, hospitalization for heart failure all SAEs, all serious CV AESI and all drug-related AEs were collected at routine and unscheduled visits and/or through minimal direct contact with participants by their health care provider.

Non-serious CV AESI and non-serious pneumonia/LRTI were also captured by the investigator in the eCRF. All other non-serious events were reported by the site investigator to GSK via national reporting systems.

Detailed documentation of all CV and cerebrovascular events of interest, serious pneumonia and serious LRTI events, other SAEs, and deaths was sought from the treating physicians, medical records, death certificates, postmortems, and other sources as available and relevant to the event of interest. Biochemical and imaging test results, including ECGs measures taken in association with CV and cerebrovascular events of interest, for diagnosis and at time of hospital discharge were obtained as available.

This documentation was used by the EAC to classify the primary safety outcomes including MI, stroke, and new onset or acute worsening/decompensation heart failure as “confirmed” or “unconfirmed” using predefined algorithms based on the endpoint definitions referenced in ANNEX 1 – Charter of the Adjudication committee.

**Table 1 Data Collection Schedule**

| Data elements | Pre-enrollment medical history[1] | Enrollment visit | Routine care visits[2] | Additional 6-month participant contact[3] | Event related participant contact | Final participant contact (study completion)[4] |
|---|---|---|---|---|---|---|
| Informed consent | | X | | | | |
| Demographics (e.g., age, gender, ethnic origin) | | X | | | | |

| Data elements | Pre-enrollment medical history[1] | Enrollment visit | Routine care visits[2] | Additional 6-month participant contact[3] | Event related participant contact | Final participant contact (study completion)[4] |
|---|---|---|---|---|---|---|
| Clinical assessments (e.g., height, weight, blood pressure) | | X | | | | |
| COPD disease severity | X | X | | | | |
| Spirometry – (e.g., $FEV_1$, FVC)[5] | X | X | X | | X | |
| History of CV and cerebrovascular diagnoses and treatments, other CV risk factors | X | X | | | | |
| Co-morbidities (e.g., diabetes, hypertension, heart disease) | X | X | X | X | | X |
| Smoking history and status | X | X | X | | | X |
| Treatment with UMEC/VI, UMEC, or TIO including prescription dates, records, & report from participant interview | | X | X | X | X | X |
| Moderate /severe COPD Exacerbations | X | | X | X | X | X |
| Concomitant medication/treatments | X | X | X | X | X | X |
| CV and cerebrovascular outcomes | X | | X | X | X | X |
| Pneumonia/ LRTI outcomes | X | | X | X | X | X |
| All-cause mortality | | | | | X | X |
| Cause of death[6] | | | | | X | X |
| SAEs | | | X | X | X | X |
| Cardiovascular adverse events | | | X | X | X | X |
| Pregnancy | | X | X | X | X | X |
| Dyspnea assessment – mMRC | | X | | | | |
| CAT | | X | | | | |

CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; CV: Cardiovascular; $FEV_1$: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; LRTI: Lower Respiratory Tract Infection; mMRC: Modified Medical Research Council; SAEs: Serious Adverse Event; TIO: Tiotropium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate; UMEC: Umeclidinium

1 Obtained from available from medical records once informed consent was obtained.

2 Data collection occurred during routine visits with treating physician once within each time window of ±90 days of each 6-month time point following study enrollment.

3 Only participants who had no recorded health care contact for a period of 6 months for whom a lack of contact was outside of normal health care practice were contacted directly by their health care practice to collect minimal information regarding safety.

4 Prior to the end of study follow-up, the participant was contacted for endpoint and safety events of interest.

5 Spirometry results i.e., $FEV_1$ and FVC were noted when the information was available as part of normal care.

6 As available e.g., from death certificates, hospital records.

### 9.5.1. Patient-reported outcomes

The PRO assessments were the mMRC dyspnea scale and the CAT. The questionnaires were completed at the enrollment visit by the participant without interference from accompanying friends, family, or medical staff. The mode of collection of the PROs was consistent across all participants and sites. Table 2 summarizes the instrument descriptions.

**Table 2 Participant-Reported Outcome Instruments**

| Instrument | Description |
|---|---|
| mMRC | The mMRC scale is a single item assessment in which participants indicate their degree of exercise-related breathlessness. Participants pick one of 5 statements that best describes their experience covering the range of dyspnea from none (Grade 0) to near complete incapacity (Grade 4) [Mahler, 1988; Hajiro, 1998]. |
| CAT | The CAT is a validated, short, and simple participant completed questionnaire which has been developed for use in routine clinical practice to measure the health status of participants with COPD. The development of the CAT has involved well accepted methodologies used to develop psychometric tools [Jones, 2009a; Jones, 2009b; Jones, 2012]. The CAT is an 8-item questionnaire suitable for completion by all participants diagnosed with COPD. When completing the questionnaire, participants rate their experience on a 6-point scale, ranging from 0 to 5 with a maximum score of 40. Higher scores indicate greater disease impact. |

CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; mMRC: modified Medical Research Council.

### 9.5.2. Baseline/enrollment

The following data elements were collected during the enrollment visit for all enrolled participants after written informed consent was obtained:

- Details of initiated COPD treatment with UMEC/VI, UMEC, or TIO including duration of prescription and dose
- Participant demographics (where feasible and permitted by country regulations)
  - Date of enrollment
  - Age
  - Gender
  - Race and ethnicity
  - Highest educational level reached
  - Predominant occupation during working age, e.g., manual/clerical/management/homemaker
  - Alcohol intake history (units/ week)
- Clinical assessments
  - Weight and height for BMI calculation
  - Systolic and diastolic blood pressure
  - NYHA Heart Failure Class
  - Most recent serum lipid values as recorded in past 12 months, including: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides
- COPD status:
  - Spirometric measures: $FEV_1$/FVC and $FEV_1$ % predicted where available from medical records
  - Age at COPD diagnosis

  - Number and severity of COPD exacerbations in past 12 months (requiring treatment with antibiotics or systemic steroids, hospitalization)
  - Treating physician assessment of disease severity i.e., stable/ unstable COPD
- Medication used to treat COPD in the past 12 months (including dates of use, form, and dosage)
- Smoking history, status (current, ex-smoker, non-smoker)
- History of CV and cerebrovascular diagnoses: diabetes mellitus, hypertension, MI/unstable angina, stroke, TIA, heart failure, tachycardia, atrial or ventricular, brady arrhythmias, cardiac arrest, left bundle branch block, and revascularization. For MI/Unstable angina, stroke, TIA, and cardiac arrest, the number of prior events were also collected
- Other co-morbidities: Prior history of asthma, LRTI, pneumonia, glaucoma, psychiatric disorders, dyslipidemia, CKD, and cancer (malignant/benign) including lung cancer. Dyslipidemia will be also assessed by collecting the most recent information on total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides each as recorded in the past 12 months
- Family history of CV and cerebrovascular diagnoses
- Concomitant medications/therapies of interest including respiratory medications in the 12 months prior to enrolment
- The following questionnaires completed by the participant at the enrollment visit:
  - mMRC dyspnea scale
  - CAT

Detailed medical history was collected at study enrollment using the eCRF. It is expected that medical history information was provided by the treating physician and based on a combination of self-reported information from the enrolled participant and, where available, supplemented by participant's electronic medical record. History of physician diagnosed co-morbidities was collected using indicator flags (Current/Past/No medical history/Not assessed).

### 9.5.3. Follow-up

The following data as far as available from routine medical practice and/or physician report from participant interview were collected for all enrolled participants at each follow-up contact:

- Change in concomitant medications including respiratory and CV medication
- Study medication exposure status from physician/medical records, including prescription records, and participant self-report
- Smoking status
- Outcomes of interest and additional data for each event of interest – additional data to be obtained from physician/medical records for reported primary CV and cerebrovascular events of interest, pneumonia and LRTI outcomes, moderate/severe COPD exacerbation, health resource utilization outcomes, SAEs, CV SAEs, including the available results of laboratory and imaging reports which were performed as standard of care for CV and cerebrovascular events

- Indicators of possible safety events of interest, e.g., hospitalizations not collected elsewhere

### 9.5.4. Discontinuation

The following data were collected for all enrolled participants at the time of discontinuation from the study:

- Date of discontinuation from the study
- Reason for discontinuation (e.g., withdrawal of consent, death, lost to follow-up) from the study

All events of interest were followed until resolution or until the end of the follow-up period, whichever came first. Discontinuation of the initiated COPD medication (UMEC/VI, UMEC, or TIO) did not affect the participant's continued participation in the study, and participants were encouraged and expected to remain in the study until the conclusion of follow-up regardless of such discontinuation.

## 9.6. Bias

Potential sources of bias inherent to the study design and measures applied to address them include the following:Channeling bias: factors associated with treatment choice (UMEC/VI, UMEC, or TIO) or with any of the study outcomes of interest (including completeness of information) were measured at enrolment and were considered through propensity score methods. These factors include indication of use, i.e., treatment choice associated with severity of disease, prescribing pattern differences across practices and countries and reimbursement differences.Healthy user bias/depletion of susceptible: long-term users of a given medication have generally shown tolerance to the drug and may be at lower risk of CV events than new users. Since participants were eligible at the time of initiation of a new medication regimen (new user study design), this is expected to limit the bias associated with the study of prevalent medication users. It is acknowledged that participants may have used a previous LAMA medication as recently as 12 months prior to study enrollment; however, this liberal definition of "new user" is intended to be inclusive to reach a representative population of participants who initiate use of UMEC/VI, UMEC, or TIO for COPD.Inconsistent interpretation of eCRFs by participating sites: might lead to differences in data collection between sites, and potential information bias between cohorts if these are not balanced between sites. To maximize consistency of eCRF interpretation, all sites underwent standardized training and utilized standardized documentation for completing case report forms at enrollment and for each follow-up assessment. Representativeness of COPD population: the study enrolled participants newly prescribed with UMEC/VI, UMEC or TIO for COPD. The selection of study sites and countries was planned to reflect this subpopulation of COPD participants initiating new treatment with UMEC/VI, UMEC, or TIO. These participants differ from the broader population of COPD participants at other stages of their treatment. While this is not a limitation or challenge to the internal validity of the study in addressing its primary and secondary objectives among participants meeting the study inclusion and exclusion criteria, it should not be noted as potential limitation to the extrapolation of the results to the broader population of COPD participants.

Follow-up bias cannot be excluded and more particularly during the COVID-19 pandemic. For example, if participants with AEs were less likely to return to the study physician for follow-up. This bias was however, mitigated by the ability to follow-up directly with participants even if they did not return to the enrolling sites.

## 9.7. Study Size

The estimated required number of events were intended to provide adequate power to demonstrate non-inferiority of UMEC/VI or UMEC, relative to TIO, for the risk of the primary endpoint based on an analysis of time to first event. The non-inferiority criterion was the upper bound of the 95% confidence interval (CI) around the hazard ratio (HR) not exceeding 2.0 and the lower bound of the 95% CI not exceeding 1.0. The primary endpoint was the composite endpoint of MI, stroke, heart failure or sudden cardiac death.

Assumptions were as follows:

- One-sided alpha 2.5%
- 90% power
- Non-inferiority margin of 2.0
- 1:1 ratio of treatment groups compared
- Events were confirmed on adjudication and occurred while the participant was on the originally prescribed treatment (add-on treatments were permitted)

The sample size calculation was applied separately to each comparison (UMEC/VI vs. TIO or UMEC vs. TIO) for the composite endpoint. Based on these assumptions, it was estimated that for each comparison made, 98 participants with an adjudicated event were required to be observed. Participants recruited were to be followed until the required number of participants with adjudicated events for the primary endpoint was observed. To convert this to an approximate number of participants, the following assumptions were used:

- Event rate per 100 person-years of 0.89 for the composite endpoint.
- Mean follow-up time (person-time) of 2.5 years.

Based on these assumptions, an estimated sample size of approximately 2233 participants per treatment cohort was required for the primary endpoint analysis yielding a total required sample size of approximately 6700 total evaluable participants.

## 9.8. Data transformation

A data management plan was created before data collection began and described all functions, processes, and specifications for data collection, cleaning and validation. Data quality was enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data. The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the plan. Ad hoc queries were generated within the electronic data capture (EDC) system and followed-up for resolution. High data quality standards were

maintained, and processes and procedures utilized to repeatedly ensure that the data were as clean and accurate as possible when presented for analysis.

### 9.8.1. Data handling conventions

All data were collected and entered directly into the EDC system. Sites were responsible for entering extracted participant data into a secure internet-based EDC database via the eCRF (see ANNEX 1 – Sample Case Report Form). All participating sites had access to the data entered regarding the individual site's own enrolled participants. All sites were fully trained in using the on-line data capture system, including eCRF completion guidelines and help files. Investigators and site personnel were able to access their account with a unique username and password. All eCRFs were completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRFs were reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs were documented in an audit trail and an adequate explanation was provided. All participating sites had access to the data entered by the individual site on their own enrolled participants through the EDC system.

#### 9.8.1.1. Clinical Event Validation and Adjudication

The EAC was blinded to exposure status regarding treatment with UMEC/VI, UMEC, or TIO. In the context of an observational study, no medical follow-up or specific diagnostic procedures was mandated outside of usual care, and thus available evidence for clinical confirmation of events was limited to that available from participant medical records, death certificates, postmortems, and discussion during visits with the treating physician. Serious pneumonia and serious LRTI outcomes were considered confirmed on the basis of diagnosis by the treating physician and were not adjudicated by the EAC. Deaths were considered confirmed based on the diagnosis by the treating physician and/or death certificate. The EAC also determined CV versus non-CV death based on death certificate information and other documentation as available.

Events recorded in EDC were compared with the electronic adjudication system (EAS). Once events completed adjudication and were entered in the EAS, they could not be deleted, which leads to discrepancies between the EAS and EDC (when the EDC was updated after investigators submitted observed events). Events were recorded as irreconcilable events if it is not possible to reconcile the data between EDC and EAS.

### 9.8.2. Resourcing needs

Biostatistical and methodological issues were addressed by the CCI biostatistician and epidemiologist with expertise in observational research responsible for the study, in consultation with a senior level statistician at GSK, who contributed to the development of the protocol and provided expertise and skills as needed during the conduct and analysis of the study.

The analysis was independently conducted by CCI programmers under the guidance of CCI biostatistics team skilled in population-based analyses using Statistical Analysis Software (SAS) v.9.4.

## 9.9. Statistical methods

A detailed Statistical Analysis Plan (SAP) was prepared and finalized prior to the conduct of this analysis. Full details on data transformations/derivations, categorical definitions, analyses, handling of missing data, and presentation of results was described separately in the SAP (ANNEX 1- Statistical Analysis Plan [SAP]).

### 9.9.1. Main summary measures

Descriptive analyses

The demographic and clinical profiles of the study population were described using data collected from the medical history during the pre-enrollment period and at the time of the enrollment visit. Additionally, the balance in measured covariates between cohorts based on propensity scores (PS) was assessed using the average standardized absolute mean difference approach. For each characteristic, the standardized difference (Std Diff) between those exposed to UMEC versus TIO or those exposed to UMEC/VI versus TIO was provided. 'Not assessed' was considered a category when calculating the differences for categorical variables because differences there could be important indicators of response biases. Further information was collected throughout the follow-up. Concomitant use of ICS was of particular interest as a potential indicator of COPD severity, its worsening or lack of control.

Exposure switch and add-on of COPD medications

Information on the first change following prescription index date for participants who were not taking a concomitant COPD maintenance therapy at the time of the index prescription was presented, including the first exposure switch/discontinuation and add-on medications by cohort, augmentation with ICS and/or LABA during observation period, reason for exposure discontinuation, and duration of index exposure. Treatment patterns were considered when estimating the PS.

Observed and confirmed events

CV and cerebrovascular events including MI, stroke, and new onset or acute worsening/decompensation heart failure, and death, were initially identified by the investigator and were referred to as observed events. All observed events were submitted for adjudication by the EAC to determine whether a given CV event could be considered confirmed. Primary analyses of CV events used confirmed events, however, a sensitivity analysis of investigator-reported events (regardless of confirmation) was performed.

Deaths were also adjudicated and categorized further by the EAC as CV-related versus non-CV related. If necessary, a third category, "undetermined", was used by the EAC for deaths that could not be clearly classified as CV-related or not.

### 9.9.2. Main statistical methods

Enrolled patients (ENR) population

All screened participants that provided consent, met all inclusion and exclusion criteria, and enrolled were included in this population. This population includes all participants regardless of subsequent withdrawal from the study, loss to follow-up, death, or termination of study for any cause.

Full analysis set (FAS) population

The FAS population was defined as participants with 1 or more post-baseline contacts. The FAS also excluded participants in sites with principal investigator (PI)-unsigned casebooks.

Propensity scores (PS)

PS were used as a weighting factor to adjust for differences in baseline covariate balance between treatment groups. PS were estimated separately for each treatment comparison (UMEC versus TIO and UMEC/VI versus TIO) using logistic regression to compute a predicted probability of initiating UMEC or UMEC/VI versus TIO [Rosenbaum, 1983; Stürmer, 2006]. All baseline variables described in Section 9.4 9.4were evaluated, and variables identified as potential instruments were examined in bivariate analyses to determine whether they were potentially related to the exposure only but not the primary outcomes directly or indirectly and would therefore be considered an instrument of exposure receipt. In this case, the variables were excluded from the PS, as adjustment for these variables had been shown to decrease precision of the estimate.

Due to the large number of variables being considered, the impact of missing data was evaluated and handled accordingly as described in SAP Section 5.5.1. The following variables were excluded from the model due to high proportion of missingness:

- NYHA risk score
- History of tachycardia
- Systolic BP
- Diastolic BP
- Total cholesterol
- LDL-cholesterol
- HDL-cholesterol
- Triglycerides
- Number of angina episodes resulting in hospitalization

Separate PS were created for each of the 2 planned comparisons (UMEC versus TIO; and UMEC/VI versus TIO). The final PS model had the advantage of having the same variables in each exposure comparison.

Inverse probability of treatment weighting

The estimated PS were used to ensure treatment cohorts are balanced on PS using stabilized inverse probability of treatment weighting (IPTW). IPTW was derived from the predicted probability of exposure I as 1/e for treated (i.e., UMEC or UMEC/VI) participants and 1/(1-e) for untreated (i.e., TIO) participants. Different sets of weights were derived for each

of the 2 exposure comparisons. To obtain appropriate estimates of the variance of the treatment effect, stabilized IPTWs were used, which were obtained by multiplying the IPTW by the marginal probability of treatment (for the treated) and one minus the marginal probability of treatment (for the untreated).

Propensity score matched (PSM) cohorts' population

The propensity score matched (PSM) cohorts were used for analyses of incidence rates and frequency counts. Separate PSM cohorts were created for the 2 planned comparisons (UMEC versus TIO; and UMEC/VI versus TIO). PSM groups were assembled using a greedy matching algorithm with a caliper set at 0.2 SDs of the PS. Participants were matching individually and participants who did not match were excluded from this population but were included in the FAS. A PSM cohort allowed for calculations of incidence rate ratios (IRR) and event rates without complex adjustments for imbalance between cohorts.

Analyses corresponding to the primary objectives

1. *To demonstrate non-inferiority of UMEC/VI combination and UMEC to TIO for risk of the composite endpoint of MI, stroke, heart failure, or sudden cardiac death based on an analysis of time to first event*

Cox proportional hazards models were used to compare the time to first composite event (MI, stroke, and new onset or acute worsening/decompensation heart failure or sudden cardiac death) from start of initiated treatment between PS balanced cohorts of UMEC/VI and TIO initiators, and between PS balanced cohorts of UMEC and TIO initiators. The HR along with 95% CI was calculated for each treatment comparison. If the upper bound of the 95% CI for the HR exceeds 2.0, the non-inferiority assumption was rejected. If the lower bound of the 95% CI was above 1.0, non-inferiority was not assumed. Kaplan-Meier curves comparing for each treatment cohort were also presented.

CCI

[redacted]

2. *To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death*

For the main analysis, only events which were confirmed upon adjudication during the follow-up period were included. The follow-up period for survival models were defined as the period between the prescription index dates until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Sensitivity analyses included stratified analyses by age, gender, concomitant use of ICS as well an application of alternative methods like matching by PS and multivariate adjustment of un-balanced cohorts, in addition to the analysis of events observed and recorded during follow-up time until the earliest of: withdrawal from the study, conclusion of study follow-up, or death.

The number and percentage of participants with the composite endpoint and the event rate per person-year were also stratified by number of prior exacerbations (0 or ≥1) in the 12 months prior to index/enrolment.

CCI [redacted]

Analyses corresponding to the secondary objectives

1. *To compare UMEC/VI combination and UMEC to TIO for risk of MI, stroke, and heart failure individually based on an analysis of time to first event*

Cox proportional hazards models were used to compare the time to first event (MI, stroke, and new onset or acute worsening/decompensation heart failure) from start of initiated treatment between PS balanced cohorts of UMEC/VI and TIO initiators, and between PS balanced cohorts of UMEC and TIO initiators. HR along with 95% CI was calculated for each treatment comparison for each endpoint.

Only events which were confirmed upon adjudication during the follow-up period were included. For the secondary analyses, the follow-up period was defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

Sensitivity analyses were performed stratified by age, gender, concomitant use of ICS as well an application of alternative methods like matching by PS and multivariate adjustment of un-balanced cohorts, in addition to the analysis of events observed and recorded during follow-up time until the earliest of: withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of each of MI, stroke, and heart failure*

The incidence rate (number of first events per person-year) of each of MI, stroke and new onset or acute worsening/decompensation heart failure were computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with 95% CI. The number and percentage of participants with each event (MI, stroke, or new onset or acute worsening/decompensation heart failure), the total number of each event and the event rate (total number of each event per person-year) were also summarized. Further, IRR accompanied by 95% CI were derived.

During the follow-up, a COPD patient could experience one or more events considered as the study outcome.

For MI, all events from the prescription index date until censoring were flagged and their distribution summarized per exposure cohort. Further, to address the primary objective, the first adjudicated event of MI from the prescription index was considered and time from new use start date to this first event ascertained. The denominator consisted of all new users. The presence of past events of MI, as collected from available participants' history, were considered as a covariate.

Identical analysis was conducted for the event of stroke. Prior history of stroke was considered as a covariate.

For newly diagnosed or acute decompensating/worsening congestive heart failure both participants with new diagnosis of congestive heart failure and acute decompensating/worsening congestive heart failure were counted. The denominator consisted of all new users. Again, prior history of heart failure was considered as a covariate.

The incidence rate (number of first events per person-year) and 95% CI of each of MI, stroke and new onset or acute worsening/decompensation heart failure were computed for the following subgroups of the TIO initiators cohort: Handihalers, Respimat, and generic. The number and percentage of participants with each event (MI, stroke, or new onset or acute worsening/decompensation heart failure), the total number of each event and the event rate (total number of each event per person-year) were also summarized for these subgroups.

Full definitions of MI, stroke and heart failure events were described in the protocol (ANNEX 1 – Protocol Amendment No. 4). All events of any of the outcomes were collected and the first event (adjudicated first event for the main analysis) of each of the outcomes flagged.

In case of a patient being diagnosed with more than one outcome, the following rule applied: For individual analysis of each of the 3 primary outcomes of stroke, MI and heart failure, a patient could contribute with their outcome into any of the 3 analyses. The first event (first adjudicated event for the main analysis) of the respective outcome was counted.

3. *To quantify the incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)*

The incidence rate (number of first events per person-year) of serious pneumonia/ serious LRTI as a composite endpoint were computed within PS balanced cohorts of UMEC/VI and TIO initiators, and between PS balanced cohorts of UMEC and TIO initiators, along with 95% CI. The number and percentage of participants with serious pneumonia/serious LRTI, the total number of serious pneumonia/serious LRTI events and the event rate (total number of events per person-year) were also summarized. Cox proportional hazards models were used to compare the time to first event (serious pneumonia or serious LRTI) from start of initiated treatment between PS balanced cohorts of UMEC/VI and TIO initiators, and between PS balanced cohorts of UMEC and TIO initiators. HR along with 95% CI was calculated for each treatment comparison.

In principle, it was expected that participants were recruited into this observational study in a stable state. Any acute LRTI/pneumonia event prior to new exposure start were recorded based on available history and accounted for in the analysis.

4. *To quantify the overall mortality rate, CV, and non-CV mortality rates*

Mortality rates (number of deaths per person-year at risk) for all-cause mortality, CV mortality, and non-CV mortality were presented by treatment and computed within PS balanced cohorts of UMEC/VI and TIO initiators, and between PS balanced cohorts of

UMEC and TIO initiators, along with 95% CIs. The number and percentage of participants who died, total number of deaths (all-cause, adjudicated CV and adjudicated non-CV and undefined) the event rate (total number of events per person-year) and incidence rate (number of first events per person-year at risk) were reported.

For this analysis, only events which were confirmed upon adjudication during the follow-up period were included.

Analyses corresponding to the safety objectives

1. *To quantify the incidence rate and frequency of hemorrhagic stroke, ischemic stroke and undefined stroke*

The incidence rate (number of first events per person-year at risk) for type of stroke events (ischemic stroke, hemorrhagic stroke and undefined stroke) were presented by treatment and computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with 95% CI. The number and percentage of participants with each event, total number of each event, the event rate (total number of events per person-year) and incidence rate (number of first events per person-year at risk) were also summarized.

The follow-up period for the safety analyses was defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of hospitalization for heart failure*

The incidence rate (number of first events per person-year at risk) of hospitalization for heart failure were presented by treatment and computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with the 95% CI. The number and percentage of participants with the event, the total number of events, the event rate and incidence rate (number of first events per person-year at risk) were also summarized.

3. *To quantify the incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs)*

The incidence rate (number of first events per person-year at risk) were presented by treatment and computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with the 95% CI. The number and percentage of participants with the event, total number of each event, the event rate (total number of events per person-year) and incidence rate (number of first events per person-year at risk) were also summarized.

AEs were summarized according to Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT.

Characteristics of participants with SAEs were summarized in a listing of individual SAE events in study reports. These characteristics included medical history including recent use of UMEC/VI, UMEC, or TIO, use of other COPD medications, exacerbations, underlying

medical conditions, respiratory and other concomitant medication use, and dosing/timing of administration of study medications and other clinically relevant events and procedures.

Characteristics of participants with drug-related AEs were reported similarly.

Case narratives were provided for each SAE and drug-related AE (ANNEX 1 – Case Narratives).

4. *To quantify the incidence rate and frequency of serious CV adverse events of special interest (CV AESIs), including transient ischemic attacks (TIAs) and angina pectoris, cardiac arrhythmias (including Torsades de pointes), acquired long QT interval, heart failure, cardiac ischemia, and hypertension*

The incidence rate (number of first events per person-year at risk) of the specified serious CV AESIs were presented by treatment and computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with 95% CI. The number and percentage of participants with each event), the total number of each event, the event rate (total number of events per person-year) and incidence rate (number of first events per person-year at risk) were also summarized.

Analyses corresponding to the effectiveness objectives

1. *To quantify persistence with study medication*

Persistence and adherence were assessed by describing treatment patterns including time to discontinuation of initiated COPD medication or switch in therapy; the PDC during follow-up and MPR.

MPR was calculated by summing the number of days supplied for all but the last prescription before the patient switched or discontinued the index medication and divided by the number of days between the first and last prescription (Note: each participant had a unique denominator). Additions to the original medication were allowed as long as the participant was still exposed to the index medication. The MPR was expressed as a percentage, with non-adherence primarily defined as MPR <80% and adherence defined as MPR ≥80%.

PDC was calculated as the number of days for which the patient had possession of the initially prescribed medication divided by the number of days in the specified time period of 364.25 days for a given 0-12-month time period.

Cox proportional hazard models were used to compare the time to (earliest of) discontinuation of initiated COPD medication (including death or withdrawal from the study) or change in COPD maintenance medication from start of initiated treatment within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators. HR along with 95% CI were calculated for each treatment comparison. Kaplan-Meier curves comparing the time to endpoint for each treatment cohort was also presented. The MPR and the PDC during follow-up based on prescription dates was also reported.

The follow-up period for the effectiveness analyses was defined as the period between the prescription index date until the earliest of: 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.

2. *To quantify the incidence rate and frequency of moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalization)*

Cox proportional hazard models were used to compare the time to first moderate/severe COPD exacerbation (requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalization) from start of initiated treatment within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators. HR along with 95% CI were calculated for each treatment comparison. Kaplan-Meier curves comparing the time to first moderate/severe exacerbation for each treatment cohort were also presented.

Incidence rate (number of first events per person-year) of moderate/severe exacerbation was computed within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with the 95% CI. The number and percentage of participants with moderate/severe COPD exacerbations and the event rate (total number of events per person-year) were also summarized.

An analysis using negative binomial regression for the total number of exacerbations requiring hospitalization was reported for the FAS. The event rate ratios along with 95% CIs was also calculated.

3. *To quantify all-cause and COPD-related health care utilization*

The IR, the number and percentage of participants with an event, the total number of events and the event rate, were calculated for hospital admission (COPD-related and all-cause), ED visits (COPD-related and all-cause) and contacts with primary and secondary care were presented by treatment and within PS balanced cohorts of UMEC/VI and TIO initiators, and within PS balanced cohorts of UMEC and TIO initiators, along with 95% CI.

<u>General considerations for data analysis</u>

All AE verbatim terms were recorded and coded using the most recent version of MedDRA. Concomitant medications were coded using a GSK validated medication dictionary. GSK suspected products (including respective components if it was a combination product) were coded using relevant product list and the Company Drug Dictionary. Non-company suspected products were coded using the Integrated Coding Dictionary System.

All computations and generation of tables, listings and data for figures were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### 9.9.3. Missing values

The number and percentage of missing data were reported for each measured variable in the study. In general, missing data were not imputed and the data were analyzed as they were recorded in the study eCRFs.

### 9.9.4. Sensitivity analyses

Sensitivity analyses for the event rates, IR, and IRR for confirmed composite events (confirmed MI, stroke, heart failure or sudden cardiac death) were conducted using the observation period, which is not censored on the end of study treatment exposure. In addition, sensitivity analyses were performed for primary outcomes focusing on the appropriateness of the IPTW method of adjusting for bias. Sensitivity analyses performed included traditional multivariate analysis using covariate adjustment and matching of cohorts with PS scores.

Traditional covariate adjustment analysis for the time to first composite endpoint was performed using each of the following confounders: ICS at baseline, add-on medication during follow-up (time-varying), primary care or specialist (pulmonologist or other), country of enrolment, age, gender, race, highest educational level reached, BMI, systolic and diastolic BP, NYHA Failure Class, $FEV_1$ % predicted, number of COPD exacerbations in past 12 months (requiring treatment with antibiotics, systemic steroids or hospitalization), medications used to treat COPD in past 12 months – categories LAMA, LABA, LAMA/LABA, ICS, ICS/LABA, other COPD medications, smoking status (current, former, never), prior history of diabetes mellitus, prior history of hypertension, prior history of MI/unstable angina, prior history of stroke, prior history of heart failure, prior history of dyslipidemia, mMRC, and CAT. Each confounder was added to a Cox regression model containing an exposure cohort indicator variable. A stepwise regression procedure was used, with each variable retained if the final p-value on that variable was no greater than 0.15. The final model included all confounders identified by this procedure. The HR and Wald 95% CIs derived from the adjusted analysis were reported. The FAS population was used without weighting to assess comparability of results with the main analysis (with IPTW weighting).

A sensitivity analysis on the risk of the composite endpoint (confirmed MI, stroke, heart failure and sudden cardiac death) with the PS-matched population was also performed. The HRs and 95% CIs estimated by the Cox model with IPTW weighting for the primary outcome were compared to the results obtained using the PS-matching method. Additionally, risk of confirmed and unconfirmed MI, stroke and heart failure was analyzed using the PSM population. HRs and 95% CIs were estimated using the Cox model for the primary outcome.

In addition, sensitivity analyses were also performed to evaluate the impact of COVID-19 on the primary endpoint, including time to first composite event (confirmed MI, stroke, heart failure or sudden cardiac death).

### 9.9.5. Amendments to the statistical analysis plan

Changes to propensity scores: Initially as per the SAP all candidate variables were cross tabulated with the outcome variable (in this case, treatment group) to identify variables with little or no variation. As analyses proceeded and changes to the datasets were made, variables that triggered a warning that the 'model fit was questionable' were examined and recoded into larger groupings to allow the logistic regression procedure to complete successfully. This generally happened when first order interactions were evaluated as these sometimes required the subdivision of already-small categories in 1 variable by rare categories in another one. The SAS system would return a warning that a quasi-complete separation of data points had been detected and the likelihood would become infinity. Re-coding of variables was required owing to data sparsity to make the logistic regression model run in SAS without errors.

The following variables were dropped from the PS calculations to assure no more than 10% of patients were missing any variables (this applies to both comparisons): NYHA score; history of tachycardia; systolic and diastolic BP; total cholesterol; LDL-cholesterol; HDL-cholesterol; triglycerides; BMI; $FEV_1$ % predicted; and the number of hospitalizations due to angina.

PS-Matching: The process described in the SAP was based on a caliper set at 0.1 standard deviation (SD) of the logit of the PS. While this creates minimum bias by assuring a tight match between the mean PS of the 2 groups being compared it also cuts down on the sample size of the resulting matched cohorts. This was particularly troublesome for the UMEC/VI vs TIO comparison. The caliper size ultimately used for both comparisons was changed from 0.1 SD to 0.2 SD.

The SAS Procedure PROC PSMATCH was used to accomplish the actual match (but not the PS derivation). SAP (Section 5.5.4) allowed for use of newer software such as PROC PSMATCH when it became available.

Limited number of steps in UMEC/VI vs TIO: for the UMEC/VI vs TIO comparison, PS model building was ultimately limited to 100 steps (i.e., the use of 100 regression terms) because more steps introduced interaction terms that resulted in data sparsity problems. When this occurred, a quasi-complete separation of data points was detected, and the likelihood became infinity.

Missing predicted $FEV_1$: The mean predicted $FEV_1$ of the FAS was used when predicted $FEV_1$ was missing.

## 9.10. Quality control

A study monitoring plan, including for-cause monitoring, that was appropriate for the study design was developed and implemented.

During the site initiation visit, the monitor provided training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. To ensure the integrity of the data, sites were monitored. Site monitoring was conducted according to the approved study monitoring plan to examine compliance with the protocol and adherence

to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents were properly maintained for the duration of the study. The monitor performed source data verification by review of original participant records.

All discrepancies during data collection are summarized in ANNEX 1 – Data Handling Report. CCI [redacted].

The monitor closed sites after the last participant's final follow-up assessment was completed, all data were entered, and all outstanding monitoring issues were resolved or addressed. Monitoring procedures and frequency of monitoring visits were described in a Clinical Operations Plan. Monitor contact details for each participating site were maintained in the Investigator Site File. Sites with unsigned casebook by the PI were closed by certified letters or remote closeout visits and were documented in the Data Handling Report Open Issues at Closed Sites (ANNEX 1 – Data Handling Report). Participants in these sites were excluded in FAS. CCI [redacted].

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities were permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the participants' original medical records. Audits could be conducted at any time during or after the study to ensure the validity and integrity of the study data.

Clinical Event Validation and Adjudication irreconcilable events

There were 39 events that were not possible to reconcile between the EDC and EAS. Detailed description of each Clinical Event Validation and Adjudication (CEVA) irreconcilable events are presented in ANNEX 2.1. From 39 irreconcilable events, 13 were identified by the EAC while reviewing documents received from sites for submitted events (despite queries issued, sites did not enter the events in the EDC). Four events were irreconcilable as participant numbers had been updated in the EDC and the events were already fully adjudicated in the EAS so the participant IDs remain mismatched. Lastly, 22 irreconcilable events were deleted (but visible in the audit trail) in the EDC but remain present in the EAS as they had completed event adjudication. The reasons for events being deleted in the EDC included: changed information (3 events); event change following adjudication (5 events); investigator judgement (1 event); new information (1 event); per query (1 event); transcription error (10 events); and updated (1 event).

# 10. RESULTS

## 10.1. Participants

A total of 6606 participants were enrolled in the study, of whom 6165 were included in the FAS (see Table 3). The FAS consisted of similar proportions of participants in the

UMEC/VI (n=2448, 39.7%) and TIO (n=2471, 40.1%) cohorts and less participants in the UMEC cohort (n=1246, 20.2%). Propensity scores (PS) were calculated for each treatment comparison. The final matched cohorts included 2228 participants in the UMEC vs TIO PSM cohort (1114 participants from UMEC and TIO each), and 2808 (1404 participants from UMEC/VI and TIO each) participants in the UMEC/VI vs TIO PSM cohort.

The number of enrolled participants decreased between the interim report and final analysis (7223 vs 6606 participants) due to participants that were not eligible, could not be unassigned to a cohort, had unsigned casebooks or participant was not a new user (see ANNEX 1 – Interim Analysis Report).

**Table 3 Participant recruitment**

| | Total | UMEC n (%) | UMEC/VI n (%) | TIO n (%) |
|---|---|---|---|---|
| All Enrolled Participants | 6606 | 1331 (20.1) | 2644 (40.0) | 2631 (39.8) |
| Full Analysis Set Population | 6165 | 1246 (20.2) | 2448 (39.7) | 2471 (40.1) |
| PS-Matched Population | | | | |
| UMEC vs TIO | 2228 | 1114 (50.0) | -- | 1114 (50.0) |
| UMEC/VI vs TIO | 2808 | -- | 1404 (50.0) | 1404 (50.0) |

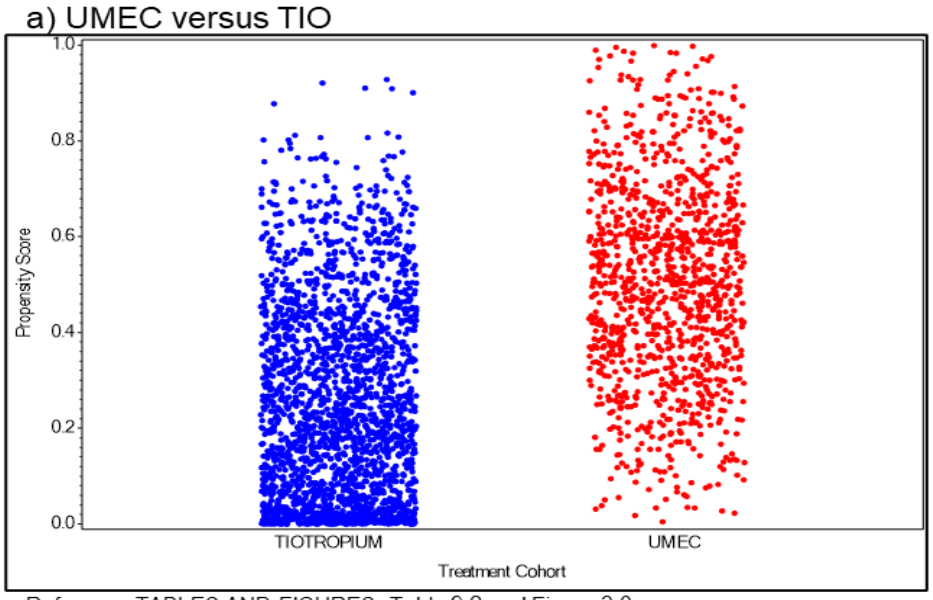
PS: propensity score; TIO: Tiotropium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate; UMEC: Umeclidinium.
Note: All percentages were based on total column.
Full Analysis Set included only enrolled participants with one or more post-baseline contact.
Reference TABLES AND FIGURES: Table 1.0

Distribution of propensity scores

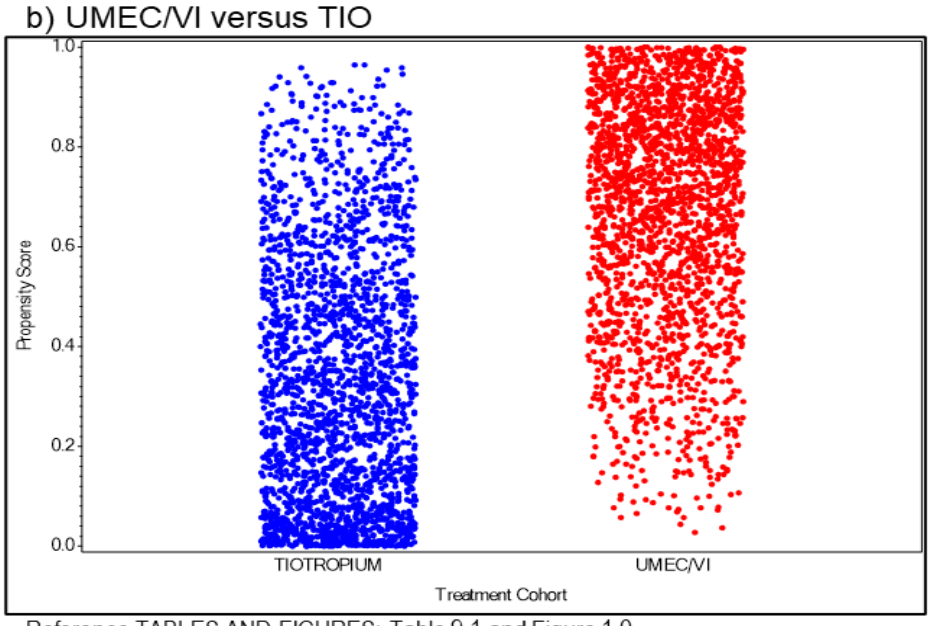
PS were calculated for each treatment comparison and further described in Section 9.9.2. Plots of PS presented in Figure 2 indicate the predicted probability of receiving UMEC or UMEC/VI rather than TIO.

The mean (SD) PS were 0.503 (0.2089) and 0.253 (0.2031) for the respective UMEC and TIO cohorts and 0.677 (0.2261) and 0.327 (0.2511) for the respective UMEC/VI and TIO cohorts (ANNEX 1 – TLFs Table 9.1 and Table 9.2). These PS results demonstrate differences in the selected baseline characteristics between the UMEC and UMEC/VI cohorts compared to the TIO cohort which resulted in a limited number of matched participants included in the PS-matched cohorts (Table 3).

**Figure 2 Plot of propensity scores**




Reference TABLES AND FIGURES: Table 9.2 and Figure 3.0




Reference TABLES AND FIGURES: Table 9.1 and Figure 1.0

TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate
The propensity mscore was the predicted probability of receiving UMEC or UMEC/VI rather than TIO.
Overlap of distributions between treatment groups was desirable.

Participants disposition

Overall, 3940 (63.9%) participants completed the study (see Section 9.3.4 for definition) and 2220 (36.0%) discontinued the study (see Table 4). The proportions of participants

discontinuing the study were similar across the cohorts: 439 (35.2%) in the UMEC cohort, 923 (37.7%) in the UMEC/VI cohort, and 858 (34.7%) in the TIO cohort. The reasons for discontinuations were also similar across cohorts with the main reasons for discontinuation in the UMEC and UMEC/VI cohorts being 'lost to follow-up' (UMEC: n=145, 33.0%; UMEC/VI: n=281, 30.4%) followed by 'withdrew consent' (UMEC: n=116, 26.4%; UMEC/VI: n=245, 26.5%), and 'death' (UMEC: n=84, 19.1%; UMEC/VI: n=215, 23.3%). This differed slightly among participants in the TIO cohort where the main reason for discontinuation was 'withdrew consent' (n=271, 31.6%) followed by 'lost to follow-up' (n=250, 29.1%), then 'death' (n=170, 19.8%).

**Table 4 Participant disposition – FAS**

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | Total (N=6165) n (%) |
|---|---|---|---|---|
| **Completed Study** [1] | 804 (64.5) | 1524 (62.3) | 1612 (65.2) | 3940 (63.9) |
| **Status Unknown** [1, 2] | 3 (0.2) | 1 (<0.1) | 1 (<0.1) | 5 (<0.1) |
| **Discontinued Study, n (%)** [1] | 439 (35.2) | 923 (37.7) | 858 (34.7) | 2220 (36.0) |
| **Reason for Discontinuation** [3] | | | | |
| Protocol Deviation | 1 (0.2) | 0 (0.0) | 2 (0.2) | 3 (0.1) |
| Adverse Event | 6 (1.4) | 18 (2.0) | 8 (0.9) | 32 (1.4) |
| Lack of Efficacy | 8 (1.8) | 16 (1.7) | 4 (0.5) | 28 (1.3) |
| Progressive Disease | 3 (0.7) | 5 (0.5) | 9 (1.0) | 17 (0.8) |
| Physician Decision | 43 (9.8) | 71 (7.7) | 78 (9.1) | 192 (8.6) |
| Withdrew Consent | 116 (26.4) | 245 (26.5) | 271 (31.6) | 632 (28.5) |
| Lost to Follow-up | 145 (33.0) | 281 (30.4) | 250 (29.1) | 676 (30.5) |
| Death | 84 (19.1) | 215 (23.3) | 170 (19.8) | 469 (21.1) |
| Site Closed | 24 (5.5) | 59 (6.4) | 35 (4.1) | 118 (5.3) |
| Study Closed/Terminated | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (<0.1) |
| Other | 9 (2.1) | 12 (1.3) | 31 (3.6) | 52 (2.3) |

CRF: Case report form; FAS: Full analysis set; TIO: Tiotropium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate; UMEC: Umeclidinium.
1 Percentages based on N in column heading.
2 For 5 participants, the End of Study form was not completed at the end of the study. These participants did not complete the prospective follow-up.
3 Percentages based on the number of participants who discontinued study.
Medication termination or switch did not cause study discontinuation.
Completed Study was derived from CRF Reason for Study Discontinuation'= 'Completed Study'. Patients may discontinue at any timepoint during the study.
Reference TABLES AND FIGURES: Table 2.0

## 10.2. Descriptive data

### 10.2.1. Baseline key characteristics

Overall, most participants were enrolled in the US (n=1167, 18.9%), Poland (n=1094, 17.7%), and Germany (n=963, 15.6%), however distributions differed across the cohorts (see Table 5). In the UMEC cohort, large proportions of participants were from the UK (n=217, 17.4%), Germany (n=206, 16.5%), and Hungary (n=161, 12.9%). Large proportions of participants in the UMEC/VI cohort were from Poland (n=694, 28.3%), Germany (n=448, 18.3%), and Czech Republic (n=359, 14.7%). Large proportions of

participants in the TIO cohort were from the US (n=693, 28.0%), UK (n=531, 21.5%), and Germany (n=309, 12.5%).

The median (Q1-Q3) age of study participants overall was 67.0 (60-73) years old. Over half of the participants in the study were male (n=3672, 59.6%). A quarter (n=1584, 25.7%) of participants completed primary school and a similar proportion (n=1375, 22.0%) completed high school as their highest educational attainment. Participants across all cohorts were predominantly White (n=5935, 96.3%). Hispanic or Latino ethnicity was more common in the TIO cohort (n=574, 23.2%) than in the UMEC (n=92, 7.4%) and UMEC/VI (n=167, 6.8%) cohorts.

Participants in the study were recruited by the prescribing physician. Most participants in the UMEC (n=925, 74.2%) and UMEC/VI cohorts (n=1857, 75.9%) were recruited by pulmonologists. About half of the of the participants in the TIO cohort were recruited by pulmonologist (n=1256, 50.8%), and the other half were recruited by their primary care physician (n=1197, 48.4%).

Among participants with available data, the mean (SD) BMI was 27.8 (6.00) $kg/m^2$. Assessment of NYHA heart failure was most common in the TIO cohort (NYHA heart failure class not assessed in 791 [32.0%] participants) where 1059 (42.9%) participants were class I (defined as having no symptoms). Participants in the UMEC/VI cohort tended to have more HF symptoms than participants in the UMEC cohort.

Among participants with available data on pre-bronchodilator spirometry results, $FEV_1$ levels were similar across cohorts with a mean (SD) of 1.63L (0.608). The UMEC and UMEC/VI cohorts had slightly lower FVC levels with a mean (SD) of 2.76 (0.914) and 2.76 (0.840), respectively compared to 2.86 (0.963) in the TIO cohort. The UMEC cohort had higher mean (SD) $FEV_1$ % predicted (62.0 [16.54]) and $FEV_1$/FVC (0.61 [0.099]) compared to the UMEC/VI ($FEV_1$ % predicted: 57.0 [17.26]; $FEV_1$/FVC: 0.58 [0.113]) and TIO cohorts ($FEV_1$ % predicted: 57.9 [16.87]; $FEV_1$/FVC: 0.58 [0.108]). Over 90% of participants in each cohort had $FEV_1$/FVC <70%.

Among participants with available data on post-bronchodilator spirometry, the UMEC cohort had the highest mean (SD) $FEV_1$ (1.76 [0.697] L), FVC (2.98 [0.996]), and $FEV_1$ % predicted (64.4 [17.68]) across the cohorts. The UMEC/VI and TIO cohorts had similar mean (SD) $FEV_1$ (1.60 [0.564] and 1.63 [0.620], respectively) and FVC (2.88 [0.912] and 2.83 [0.923], respectively). The UMEC/VI cohort had the lowest mean (SD) $FEV_1$ % predicted (57.6 [15.09]) among the cohorts. Over 93% of participants in each cohort had $FEV_1$/FVC <70% (UMEC: n=823, 93.8%; UMEC/V: n=1866; 95.7%; TIO: n=1818, 95.4%).

The time from most recent spirometry to enrolment differed across cohorts. The UMEC/VI cohort had the shortest mean (SD) duration from spirometry to enrolment (74.4 [277.72] days) followed by the UMEC cohort (84.7 [322.56] days). The TIO cohort had a notably longer mean (SD) duration from the most recent spirometry to enrolment (190.5 [552.69] days).

The median (Q1-Q3) age at COPD diagnosis was 62.0 (55-69) years and similar across all cohorts. Participants in the UMEC and UMEC/VI cohorts had similar duration between

COPD diagnosis and enrollment (UMEC: 4.1 [6.22] years; UMEC/VI: 4.4 [6.41] years), while participants in the TIO cohort had a slightly longer duration from COPD diagnosis to enrollment (4.9 [6.28] years).

Among 2526 participants with available data on COPD classifications and stages based on the GOLD 2019 criteria, the majority of participants (n=1728, 68.4%) were classified as group B (mMRC ≥2 and CAT ≥10 and not more than 1 exacerbation, not leading to hospitalization). The GOLD classification indicated more severe COPD in the UMEC/VI cohort than in the TIO (and UMEC) cohort. After reclassifying participants using the GOLD 2023 classification, the proportions in groups A and B remain unchanged, and participants in former groups C (n=9, 0.4%) and D (n=83, 3.3%) (2 or more moderate/severe exacerbations, or 1 or more leading to hospitalization) were classified into a single group E (n=92, 3.6%).

A small proportion of participants had moderate/severe COPD exacerbations and hospitalizations related to COPD exacerbations in the past 12 months prior to enrollment, which was similar across cohorts. Overall, 971 (15.8%) participants had 1 exacerbation within the past 12 months with a rate (95% CI) of 0.242 (0.230, 0.255) per person-year. In the past 12 months, 300 hospitalizations related to COPD exacerbations occurred with a rate (95% CI) of 0.049 (0.044, 0.055) per person-year. Most (n=247, 4.0%) participants were hospitalized once.

Smoking status at enrolment was similar between the UMEC/VI and TIO cohorts with approximately 45% of participants identifying as current smokers and 43% were former smokers. Participants in the UMEC cohort had a slightly higher proportion of current (n=608, 48.8%) and former smokers (n=566, 45.5%).

Approximately three-quarters of the participants (n=4496, 73.5%) reported no alcohol use at enrollment. Among those who consumed alcohol, participants in the UMEC/VI cohort consumed less alcohol (mean [SD]=5.9 [10.14] units per week) than participants in the TIO cohort (mean [SD]=9.5 [13.69] units per week). Participants in the UMEC cohort reported similar alcohol consumption as the participants in the TIO cohort (mean [SD]: 10.0 [15.12] units).

Baseline mMRC dyspnea scores were similar across cohorts with 2433 (39.7%) participants overall with a score of 1 (shortness of breath when hurrying on the level or walking up a slight hill) and 2176 (35.5%) participants had a score of 2 (walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level) [Rajala, 2017].

Baseline CAT scores were similar between the UMEC/VI and TIO cohorts where both cohorts had a mean score of 17.4 (out of 40, representing a medium impact of COPD on health status). The UMEC cohort had a lower mean (SD) CAT score of 15.9 (7.42), representing less severe impact although it is still categorized as a medium impact on health [CAT User Guide 2022].

**Table 5 Key baseline characteristics – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| **Country** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.16 | 0.19 |
| Belgium, n (%) | 22 (1.8) | 27 (1.1) | 11 (0.4) | 60 (1.0) | | |
| Czech Republic, n (%) | 155 (12.4) | 359 (14.7) | 232 (9.4) | 746 (12.1) | | |
| Germany, n (%) | 206 (16.5) | 448 (18.3) | 309 (12.5) | 963 (15.6) | | |
| Hungary, n (%) | 161 (12.9) | 126 (5.1) | 114 (4.6) | 401 (6.5) | | |
| Italy, n (%) | 71 (5.7) | 82 (3.3) | 52 (2.1) | 205 (3.3) | | |
| Netherlands, n (%) | 32 (2.6) | 82 (3.3) | 82 (3.3) | 196 (3.2) | | |
| Poland, n (%) | 166 (13.3) | 694 (28.3) | 234 (9.5) | 1094 (17.7) | | |
| Spain, n (%) | 86 (6.9) | 130 (5.3) | 213 (8.6) | 429 (7.0) | | |
| UK, n (%) | 217 (17.4) | 156 (6.4) | 531 (21.5) | 904 (14.7) | | |
| US, n (%) | 130 (10.4) | 344 (14.1) | 693 (28.0) | 1167 (18.9) | | |
| **Race/Geographic Ancestry [2] n (%)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.02 |
| African American/African | 9 (0.7) | 35 (1.4) | 44 (1.8) | 88 (1.4) | | |
| American Indian/Alaskan Native | 0 (0.0) | 1 (<0.1) | 0 (0.0) | 1 (<0.1) | | |
| Asian | 1 (<0.1) | 3 (0.1) | 6 (0.2) | 10 (0.2) | | |
| Native Hawaiian/Other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | | |
| White | 1202 (96.5) | 2356 (96.2) | 2377 (96.2) | 5935 (96.3) | | |
| Mixed race | 2 (0.2) | 6 (0.2) | 6 (0.2) | 14 (0.2) | | |
| Not permitted to collect Geographic Ancestry | 32 (2.6) | 47 (1.9) | 38 (1.5) | 117 (1.9) | | |
| **Ethnicity, n (%)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.30 | 0.31 |
| Hispanic or Latino | 92 (7.4) | 167 (6.8) | 574 (23.2) | 833 (13.5) | | |
| Not Hispanic or Latino | 1130 (90.7) | 2233 (91.2) | 1858 (75.2) | 5221 (84.7) | | |
| Unknown | 24 (1.9) | 48 (2.0) | 39 (1.6) | 111 (1.8) | | |
| **Age (Years)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.05 |
| Mean (SD) | 66.0 (9.91) | 66.0 (9.38) | 66.6 (10.08) | 66.2 (9.77) | | |
| Median | 67.0 | 66.0 | 67.0 | 67.0 | | |
| Q1-Q3 | 59-73 | 60-72 | 60-74 | 60-73 | | |
| Range | (30, 91) | (27, 98) | (26, 94) | (26, 98) | | |
| **Age Category (Years)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.04 |
| <65, n (%) | 515 (41.3) | 1020 (41.7) | 987 (39.9) | 2522 (40.9) | | |
| ≥65, n (%) | 731 (58.7) | 1428 (58.3) | 1484 (60.1) | 3643 (59.1) | | |
| 65-74, n (%) | 475 (65.0) | 1000 (70.0) | 933 (62.9) | 2408 (66.1) | | |
| 75-84, n (%) | 236 (32.3) | 392 (27.5) | 477 (32.1) | 1105 (30.3) | | |
| 85+, n (%) | 20 (2.7) | 36 (2.5) | 74 (5.0) | 130 (3.6) | | |
| **Gender** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.08 |
| Female, n (%) | 540 (43.3) | 921 (37.6) | 1032 (41.8) | 2493 (40.4) | | |
| Male, n (%) | 706 (56.7) | 1527 (62.4) | 1439 (58.2) | 3672 (59.6) | | |
| **Education, n (%)** | | | | | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| n | 1246 | 2448 | 2471 | 6165 | 0.11 | 0.05 |
| Primary School | 275 (22.1) | 678 (27.7) | 631 (25.5) | 1584 (25.7) | | |
| Some High School | 141 (11.3) | 358 (14.6) | 347 (14.0) | 846 (13.7) | | |
| High School Complete | 252 (20.2) | 483 (19.7) | 622 (25.2) | 1357 (22.0) | | |
| Technical/Post-Secondary | 135 (10.8) | 332 (13.6) | 290 (11.7) | 757 (12.3) | | |
| University Graduate or more | 70 (5.6) | 156 (6.4) | 164 (6.6) | 390 (6.3) | | |
| Not Assessed | 373 (29.9) | 441 (18.0) | 417 (16.9) | 1231 (20.0) | | |
| **Predominant Occupation[3] n (%)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.09 | 0.05 |
| Manual | 529 (42.5) | 1126 (46.0) | 1145 (46.3) | 2800 (45.4) | | |
| Clerical | 92 (7.4) | 247 (10.1) | 222 (9.0) | 561 (9.1) | | |
| Management | 90 (7.2) | 209 (8.5) | 186 (7.5) | 485 (7.9) | | |
| Homemaker | 63 (5.1) | 141 (5.8) | 179 (7.2) | 383 (6.2) | | |
| Other | 154 (12.4) | 405 (16.5) | 349 (14.1) | 908 (14.7) | | |
| Not Assessed | 318 (25.5) | 320 (13.1) | 390 (15.8) | 1028 (16.7) | | |
| **Physician Specialty** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.36 | 0.42 |
| Pulmonologist, n (%) | 925 (74.2) | 1857 (75.9) | 1256 (50.8) | 4038 (65.5) | | |
| Primary Care Physician, n (%) | 302 (24.2) | 527 (21.5) | 1197 (48.4) | 2026 (32.9) | | |
| Other, n (%) | 19 (1.5) | 64 (2.6) | 18 (0.7) | 101 (1.6) | | |
| **BMI** | | | | | | |
| n | 1171 | 2387 | 2396 | 5954 | 0.04 | <0.01 |
| Mean (SD) | 27.6 (5.95) | 27.8 (6.11) | 27.8 (5.91) | 27.8 (6.00) | | |
| Median | 26.7 | 27.1 | 27.3 | 27.1 | | |
| Q1-Q3 | 24-31 | 24-31 | 24-31 | 24-31 | | |
| Range | (15, 53) | (14, 63) | (14, 64) | (14, 64) | | |
| BMI <18.5 kg/m$^2$, n (%) | 39 (3.3) | 70 (2.9) | 73 (3.0) | 182 (3.1) | | |
| BMI ≥18.5 to <25 kg/m$^2$, n (%) | 371 (31.7) | 763 (32.0) | 698 (29.1) | 1832 (30.8) | | |
| BMI ≥25 to <30 kg/m$^2$, n (%) | 418 (35.7) | 804 (33.7) | 867 (36.2) | 2089 (35.1) | | |
| BMI ≥30 kg/m$^2$, n (%) | 343 (29.3) | 750 (31.4) | 758 (31.6) | 1851 (31.1) | | |
| **Systolic Blood Pressure (mmHg)** | | | | | | |
| n | 1043 | 2173 | 2260 | 5476 | 0.09 | 0.14 |
| Mean (SD) | 132.8 (15.29) | 133.7 (15.01) | 131.5 (15.52) | 132.6 (15.30) | | |
| Median | 131.0 | 133.0 | 130.0 | 130.0 | | |
| Q1-Q3 | 120-140 | 124-141 | 120-140 | 121-140 | | |
| Range | (90, 192) | (85, 200) | (84, 220) | (84, 220) | | |
| **Diastolic Blood Pressure (mmHg)** | | | | | | |
| n | 1043 | 2173 | 2260 | 5476 | 0.08 | 0.07 |
| Mean (SD) | 78.8 (9.11) | 78.7 (9.48) | 78.0 (9.42) | 78.5 (9.39) | | |
| Median | 80.0 | 80.0 | 80.0 | 80.0 | | |
| Q1-Q3 | 72-85 | 72-85 | 70-84 | 71-85 | | |
| Range | (55, 115) | (49, 140) | (47, 115) | (47, 140) | | |
| **NYHA Heart Failure Class, n (%)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.17 | 0.12 |
| I | 439 (35.2) | 844 (34.5) | 1059 (42.9) | 2342 (38.0) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| II | 138 (11.1) | 390 (15.9) | 466 (18.9) | 994 (16.1) | | |
| III | 49 (3.9) | 108 (4.4) | 144 (5.8) | 301 (4.9) | | |
| IV | 4 (0.3) | 6 (0.2) | 11 (0.4) | 21 (0.3) | | |
| Not assessed | 616 (49.4) | 1100 (44.9) | 791 (32.0) | 2507 (40.7) | | |
| **Total Cholesterol (mmol/L)** | | | | | | |
| n | 312 | 559 | 1105 | 1976 | <0.01 | 0.07 |
| Mean (SD) | 4.93 (1.114) | 4.85 (1.174) | 4.93 (1.124) | 4.91 (1.137) | | |
| Median | 4.90 | 4.81 | 4.86 | 4.86 | | |
| Q1-Q3 | 4.2-5.6 | 4.0-5.6 | 4.2-5.6 | 4.1-5.6 | | |
| Range | (2.4, 9.9) | (1.9, 7.9) | (0.5, 10.4) | (0.5, 10.4) | | |
| <5.17 (Normal), n (%) | 182 (58.3) | 345 (61.7) | 652 (59.0) | 1179 (59.7) | | |
| 5.17-<6.21 (Borderline High), n (%) | 94 (30.1) | 139 (24.9) | 318 (28.8) | 551 (27.9) | | |
| 6.21+ (High), n (%) | 36 (11.5) | 75 (13.4) | 135 (12.2) | 246 (12.4) | | |
| **LDL-Cholesterol (mmol/L)** | | | | | | |
| n | 262 | 467 | 1015 | 1744 | 0.01 | 0.03 |
| Mean (SD) | 2.81 (0.885) | 2.78 (1.027) | 2.81 (0.935) | 2.80 (0.953) | | |
| Median | 2.75 | 2.69 | 2.79 | 2.76 | | |
| Q1-Q3 | 2.1-3.4 | 2.0-3.5 | 2.1-3.4 | 2.1-3.4 | | |
| Range | (0.8, 6.1) | (0.3, 5.7) | (0.5, 5.8) | (0.3, 6.1) | | |
| <3.36 (Normal), n (%) | 192 (73.3) | 337 (72.2) | 736 (72.5) | 1265 (72.5) | - | - |
| 3.36-<4.14 (Borderline), n (%) | 50 (19.1) | 75 (16.1) | 200 (19.7) | 325 (18.6) | | |
| 4.14-<4.91 (High), n (%) | 18 (6.9) | 43 (9.2) | 60 (5.9) | 121 (6.9) | | |
| 4.91+ (Very High), n (%) | 2 (0.8) | 12 (2.6) | 19 (1.9) | 33 (1.9) | | |
| **HDL-Cholesterol (mmol/L)** | | | | | | |
| n | 287 | 508 | 1063 | 1858 | 0.15 | 0.01 |
| Mean (SD) | 1.49 (0.531) | 1.41 (0.447) | 1.41 (0.509) | 1.42 (0.497) | | |
| Median | 1.37 | 1.35 | 1.32 | 1.34 | | |
| Q1-Q3 | 1.1-1.8 | 1.1-1.6 | 1.1-1.6 | 1.1-1.7 | | |
| Range | (0.6, 4.6) | (0.5, 3.9) | (0.0, 4.6) | (0.0, 4.6) | | |
| <1.03 (Low), n (%) | 36 (12.5) | 88 (17.3) | 216 (20.3) | 340 (18.3) | - | - |
| 1.03+ (Normal), n (%) | 251 (87.5) | 420 (82.7) | 847 (79.7) | 1518 (81.7) | | |
| **Triglycerides (mmol/L)** | | | | | | |
| n | 295 | 505 | 1059 | 1859 | 0.06 | 0.13 |
| Mean (SD) | 1.61 (1.062) | 1.55 (0.830) | 1.67 (0.954) | 1.63 (0.941) | | |
| Median | 1.36 | 1.36 | 1.42 | 1.40 | | |
| Q1-Q3 | 0.99-1.91 | 1.01-1.84 | 1.06-2.05 | 1.02-1.98 | | |
| Range | (0.02, 9.40) | (0.01, 6.80) | (0.01, 11.00) | (0.01, 11.00) | | |
| ≤1.69 (Normal), n (%) | 197 (66.8) | 342 (67.7) | 659 (62.2) | 1198 (64.4) | - | - |
| >1.69 (High), n (%) | 98 (33.2) | 163 (32.3) | 400 (37.8) | 661 (35.6) | | |
| **Pre-Bronchodilator:** | | | | | | |
| **$FEV_1$ (L)** | | | | | | |
| n | 289 | 404 | 444 | 1137 | 0.02 | 0.10 |
| Mean (SD) | 1.66 (0.608) | 1.59 (0.575) | 1.65 (0.636) | 1.63 (0.608) | | |
| Median | 1.57 | 1.54 | 1.59 | 1.57 | | |
| Q1-Q3 | 1.21-2.01 | 1.17-1.94 | 1.19-2.03 | 1.19-1.98 | | |
| Range | (0.49, 4.72) | (0.08, 4.10) | (0.29, 5.80) | (0.08, 5.80) | | |
| **FVC** | | | | | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| n | 284 | 398 | 435 | 1117 | 0.11 | 0.11 |
| Mean (SD) | 2.76 (0.914) | 2.76 (0.840) | 2.86 (0.963) | 2.80 (0.909) | | |
| Median | 2.75 | 2.62 | 2.76 | 2.70 | | |
| Q1-Q3 | 2.11-3.32 | 2.17-3.27 | 2.10-3.45 | 2.12-3.35 | | |
| Range | (0.88, 7.26) | (1.13, 6.16) | (0.71, 7.70) | (0.71, 7.70) | | |
| **$FEV_1$ % Predicted** | | | | | | |
| n | 282 | 392 | 439 | 1113 | 0.24 | 0.05 |
| Mean (SD) | 62.0 (16.54) | 57.0 (17.26) | 57.9 (16.87) | 58.6 (17.03) | | |
| Median | 62.0 | 56.0 | 59.0 | 59.0 | | |
| Q1-Q3 | 51-72 | 46-69 | 47-68 | 47-69 | | |
| Range | (22, 112) | (18, 120) | (14, 113) | (14, 120) | | |
| **$FEV_1$/FVC** | | | | | | |
| n | 283 | 398 | 435 | 1116 | 0.27 | 0.02 |
| Mean (SD) | 0.61 (0.099) | 0.58 (0.113) | 0.58 (0.108) | 0.58 (0.108) | | |
| Median | 0.63 | 0.59 | 0.59 | 0.60 | | |
| Q1-Q3 | 0.55-0.67 | 0.51-0.66 | 0.51-0.66 | 0.52-0.66 | | |
| Range | (0.25, 0.97) | (0.06, 0.95) | (0.15, 0.89) | (0.06, 0.97) | | |
| $FEV_1$/FVC <70%, n (%) | 255 (90.1) | 362 (91.0) | 400 (92.0) | 1017 (91.1) | 0.06 | 0.04 |
| $FEV_1$/FVC 70% or greater, n (%) | 28 (9.9) | 36 (9.0) | 35 (8.0) | 99 (8.9) | | |
| **Post-Bronchodilator:** | | | | | | |
| **$FEV_1$ (L)** | | | | | | |
| n | 881 | 1952 | 1913 | 4746 | 0.21 | 0.04 |
| Mean (SD) | 1.76 (0.697) | 1.60 (0.564) | 1.63 (0.620) | 1.64 (0.616) | | |
| Median | 1.68 | 1.54 | 1.51 | 1.55 | | |
| Q1-Q3 | 1.28-2.10 | 1.19-1.94 | 1.19-1.99 | 1.21-2.00 | | |
| Range | (0.42, 9.20) | (0.30, 5.30) | (0.08, 4.80) | (0.08, 9.20) | | |
| **FVC** | | | | | | |
| n | 877 | 1949 | 1905 | 4731 | 0.16 | 0.05 |
| Mean (SD) | 2.98 (0.996) | 2.88 (0.912) | 2.83 (0.923) | 2.88 (0.934) | | |
| Median | 2.87 | 2.76 | 2.70 | 2.75 | | |
| Q1-Q3 | 2.29-3.52 | 2.19-3.47 | 2.17-3.38 | 2.20-3.45 | | |
| Range | (0.83, 10.10) | (0.53, 6.03) | (0.23, 7.55) | (0.23, 10.10) | | |
| **$FEV_1$ % Predicted** | | | | | | |
| n | 819 | 1879 | 1846 | 4544 | 0.32 | 0.09 |
| Mean (SD) | 64.4 (17.68) | 57.6 (15.09) | 59.1 (16.57) | 59.4 (16.36) | | |
| Median | 64.0 | 58.0 | 59.0 | 60.0 | | |
| Q1-Q3 | 54-76 | 48-67 | 48-69 | 49-69 | | |
| Range | (17, 136) | (11, 126) | (3, 112) | (3, 136) | | |
| **$FEV_1$/FVC** | | | | | | |
| n | 877 | 1949 | 1905 | 4731 | 0.13 | 0.13 |
| Mean (SD) | 0.59 (0.096) | 0.56 (0.104) | 0.57 (0.107) | 0.57 (0.104) | | |
| Median | 0.61 | 0.57 | 0.60 | 0.59 | | |
| Q1-Q3 | 0.53-0.66 | 0.49-0.64 | 0.51-0.65 | 0.50-0.65 | | |
| Range | (0.28, 0.93) | (0.15, 1.00) | (0.12, 0.99) | (0.12, 1.00) | | |
| $FEV_1$/FVC <70%, n (%) | 823 (93.8) | 1866 (95.7) | 1818 (95.4) | 4507 (95.3) | 0.07 | 0.02 |
| $FEV_1$/FVC 70% or greater, n (%) | 54 (6.2) | 83 (4.3) | 87 (4.6) | 224 (4.7) | | |
| **Time from Spirometry to Enrollment (Days)** [4] | | | | | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| n | 1240 | 2430 | 2469 | 6139 | 0.19 | 0.21 |
| Mean (SD) | 84.7 (322.56) | 74.4 (277.72) | 190.5 (552.69) | 123.2 (421.20) | | |
| Median | 0.0 | 0.0 | 6.0 | 1.0 | | |
| Q1-Q3 | 0-15 | 0-15 | 0-94 | 0-30 | | |
| Range | (0, 4162) | (-17, 4184) | (-9, 5932) | (-17, 5932) | | |
| **Years Since COPD Diagnosis** | | | | | | |
| n | 1240 | 2427 | 2465 | 6132 | 0.13 | 0.08 |
| Mean (SD) | 4.1 (6.22) | 4.4 (6.41) | 4.9 (6.28) | 4.5 (6.33) | | |
| Median | 1.0 | 2.0 | 3.0 | 2.0 | | |
| Q1-Q3 | 0-6 | 0-6 | 0-8 | 0-7 | | |
| Range | (0, 58) | (0, 60) | (0, 61) | (0, 61) | | |
| **Age at COPD Diagnosis** | | | | | | |
| n | 1240 | 2427 | 2465 | 6132 | 0.02 | <0.01 |
| Mean (SD) | 61.9 (10.78) | 61.7 (10.59) | 61.7 (10.77) | 61.7 (10.70) | | |
| Median | 62.0 | 62.0 | 62.0 | 62.0 | | |
| Q1-Q3 | 55-70 | 55-69 | 55-69 | 55-69 | | |
| Range | (20, 89) | (20, 92) | (18, 89) | (18, 92) | | |
| **GOLD 2019 Classification** | | | | | | |
| n | 554 | 982 | 990 | 2526 | | |
| Grade 1, n (%) | 108 (19.5) | 102 (10.4) | 150 (15.2) | 360 (14.3) | 0.08 | 0.08 |
| Grade 2, n (%) | 428 (77.3) | 836 (85.1) | 810 (81.8) | 2074 (82.1) | | |
| Grade 3, n (%) | 13 (2.3) | 40 (4.1) | 27 (2.7) | 80 (3.2) | | |
| Grade 4, n (%) | 5 (0.9) | 4 (0.4) | 3 (0.3) | 12 (0.5) | | |
| | | | | | | |
| Group A, n (%) | 182 (32.9) | 233 (23.7) | 291 (29.4) | 706 (27.9) | 0.05 | 0.09 |
| Group B, n (%) | 354 (63.9) | 705 (71.8) | 669 (67.6) | 1728 (68.4) | | |
| Group C, n (%) | 1 (0.2) | 7 (0.7) | 1 (0.1) | 9 (0.4) | | |
| Group D, n (%) | 17 (3.1) | 37 (3.8) | 29 (2.9) | 83 (3.3) | | |
| **GOLD 2023 Classification** | | | | | | |
| n | 554 | 982 | 990 | 2526 | | |
| Group A, n (%) | 182 (32.9) | 233 (23.7) | 291 (29.4) | 706 (27.9) | 0.05 | 0.10 |
| Group B, n (%) | 354 (63.9) | 705 (71.8) | 669 (67.6) | 1728 (68.4) | | |
| Group E, n (%) | 18 (3.2) | 44 (4.5) | 30 (3.0) | 92 (3.6) | | |
| **Number of Moderate/Severe COPD Exacerbations[5], past 12 Months** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.04 |
| 0 events, n (%) | 982 (78.8) | 2007 (82.0) | 2002 (81.0) | 4991 (81.0) | | |
| 1 event, n (%) | 222 (17.8) | 380 (15.5) | 369 (14.9) | 971 (15.8) | | |
| 2 events, n (%) | 27 (2.2) | 36 (1.5) | 63 (2.5) | 126 (2.0) | | |
| 3+ events, n (%) | 15 (1.2) | 25 (1.0) | 37 (1.5) | 77 (1.2) | | |
| Total number of events | 328 | 539 | 626 | 1493 | | |
| Range (min, max) | (0, 6) | (0, 6) | (0, 8) | (0, 8) | | |
| Rate per person-year | 0.263 | 0.220 | 0.253 | 0.242 | | |
| 95% CI | (0.236, 0.293) | (0.202, 0.240) | (0.234, 0.274) | (0.230, 0.255) | | |
| **Number of COPD Exacerbation- related Hospitalizations, past 12 months** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.04 |
| 0, n (%) | 1190 (95.5) | 2323 (94.9) | 2381 (96.4) | 5894 (95.6) | | |
| 1, n (%) | 52 (4.2) | 115 (4.7) | 80 (3.2) | 247 (4.0) | | |
| 2, n (%) | 4 (0.3) | 8 (0.3) | 9 (0.4) | 21 (0.3) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| 3, n (%) | 0 (0.0) | 1 (<0.1) | 1 (<0.1) | 2 (<0.1) | | |
| 4+, n (%) | 0 (0.0) | 1 (<0.1) | 0 (0.0) | 1 (<0.1) | | |
| Total number of Hospitalizations | 60 | 139 | 101 | 300 | | |
| Range (min, max) | (0, 2) | (0, 5) | (0, 3) | (0, 5) | | |
| Rate per person-year | 0.048 | 0.057 | 0.041 | 0.049 | | |
| 95% CI | (0.037, 0.062) | (0.048, 0.067) | (0.034, 0.050) | (0.044, 0.055) | | |
| **Smoking Status at Enrollment** | | | | | | |
| n | 1246 | 2447 | 2470 | 6163 | 0.12 | 0.05 |
| Never, n (%) | 72 (5.8) | 224 (9.2) | 301 (12.2) | 597 (9.7) | | |
| Current, n (%) | 608 (48.8) | 1136 (46.4) | 1112 (45.0) | 2856 (46.3) | | |
| Former, n (%) | 566 (45.4) | 1087 (44.4) | 1057 (42.8) | 2710 (44.0) | | |
| **Alcohol Use at Enrolment** | | | | | | |
| n | 1237 | 2437 | 2441 | 6115 | 0.04 | 0.11 |
| Yes, n (%) | 335 (27.1) | 580 (23.8) | 704 (28.8) | 1619 (26.5) | | |
| No, n (%) | 902 (72.9) | 1857 (76.2) | 1737 (71.2) | 4496 (73.5) | | |
| **Alcohol - Units per Week [6]** | | | | | | |
| N | 333 | 578 | 703 | 1614 | 0.04 | 0.26 |
| Mean (SD) | 10.0 (15.12) | 5.9 (10.14) | 9.5 (13.69) | 8.3 (12.98) | | |
| Median | 4.0 | 2.4 | 4.0 | 3.0 | | |
| Q1-Q3 | 2-12 | 1-7 | 1-12 | 1-10 | | |
| Range | (0, 140) | (0, 154) | (0, 90) | (0, 154) | | |
| **mMRC** | | | | | | |
| n | 1235 | 2436 | 2464 | 6135 | 0.04 | 0.05 |
| Mean (SD) | 1.5 (0.91) | 1.6 (0.88) | 1.5 (0.89) | 1.6 (0.89) | | |
| Median | 1.0 | 2.0 | 1.0 | 2.0 | | |
| Q1-Q3 | 1-2 | 1-2 | 1-2 | 1-2 | | |
| Range | (0, 4) | (0, 4) | (0, 4) | (0, 4) | | |
| **mMRC Scores** | | | | | | |
| 0, n (%) | 135 (10.9) | 232 (9.5) | 259 (10.5) | 626 (10.2) | | |
| 1, n (%) | 527 (42.7) | 927 (38.1) | 979 (39.7) | 2433 (39.7) | | |
| 2, n (%) | 398 (32.2) | 909 (37.3) | 869 (35.3) | 2176 (35.5) | | |
| 3, n (%) | 154 (12.5) | 345 (14.2) | 331 (13.4) | 830 (13.5) | | |
| 4, n (%) | 21 (1.7) | 23 (0.9) | 26 (1.1) | 70 (1.1) | | |
| **CAT** | | | | | | |
| n | 1236 | 2430 | 2459 | 6125 | 0.20 | <0.01 |
| Mean (SD) | 15.9 (7.42) | 17.4 (7.57) | 17.4 (7.61) | 17.1 (7.58) | | |
| Median | 15.0 | 17.0 | 17.0 | 17.0 | | |
| Q1-Q3 | 11-21 | 12-22 | 12-23 | 11-22 | | |
| Range | (0, 40) | (0, 40) | (0, 40) | (0, 40) | | |
| **CAT Scores** | | | | | | |
| CAT Score 0-10, n (%) | 307 (24.8) | 475 (19.5) | 491 (20.0) | 1273 (20.8) | | |
| CAT Score 11-20, n (%) | 606 (49.0) | 1144 (47.1) | 1113 (45.3) | 2863 (46.7) | | |
| CAT Score 21-30, n (%) | 276 (22.3) | 693 (28.5) | 743 (30.2) | 1712 (28.0) | | |
| CAT Score 31-40, n (%) | 47 (3.8) | 118 (4.9) | 112 (4.6) | 277 (4.5) | | |

BMI: body mass index; CAT: COPD Assessment Test; COPD: Chronic obstructive pulmonary disease; eCRF: Electronic case report form; FAS: Full analysis set; $FEV_1$: Forced Expiratory Volume in one Second; FVC: Forced Vital Capacity; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; mMRC: Modified Medical Research Council; NYHA: New York Heart Association; Q1: First quartile; Q3: Third quartile; SAP: Statistical analysis plan; SD: Standard Deviation; Std Diff: Standard difference; TIO: Tiotropium; UK: United Kingdom; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate; US: United States
Notes: Percentages based on the number of non-missing responses (n).
1 Std Diff was the standardized difference between those exposed to UMEC vs. tiotropium or those exposed to UMEC/VI vs. tiotropium. The standardized difference was the raw difference between groups divided by the standard deviation of the specific measure in the tiotropium group. Additional details are contained in the SAP.
2 Participants could indicate more than one race, in this case they were reported as 'mixed race'.
3 Occupation during working age.
4 Not all participants with known time from spirometry to enrollment had all spirometry results reported.
5 COPD exacerbations requiring treatment with antibiotics, systemic steroids, and/or hospitalization.
6 Guidance on alcohol intake was provided as: 1 unit = 1 glass of wine; 1.4 units = 1 dose of spirit; 1.25 units = half pint (25 cl) of beer. Additionally, eCRF completion guidelines note: US = 1.5oz hard liquor, 1 beer, 4oz wine (or metric equivalent); UK 1 unit= 1 measure of spirit, 1/2 pint beer, 1 small glass of wine (125ml) (or metric equivalent).
Reference TABLES AND FIGURES: Table 3.0, Table 4.0, and Table 7.0

### 10.2.2. Medications and therapies at baseline

Prior COPD medications

Overall, 2381 (38.6%) participants did not use COPD medications within the 12 months prior to initiating the study medication (see Table 6). The UMEC and UMEC/VI cohorts had notably higher proportion of participants without COPD medication use in the last 12 months (UMEC: n=493 [39.6%]; UMEC/VI: n=1072 [43.8%]) compared to the TIO cohort (n=816, 33.0%).

A total of 1059 (17.2%) participants received LABA monotherapy prior to their study medication. Use of prior LABA monotherapy was similar between UMEC and TIO cohorts at approximately 15% (UMEC: n=177, 14.2%; TIO: n=367, 14.9%) and more frequent in the UMEC/VI cohort (n=515, 21.0%).

A total of 1161 (18.8%) participants received an ICS/LABA fixed combination prior to their study medication. Approximately a quarter of UMEC (n=292, 23.4%) and TIO (n=625, 25.3%) cohorts used ICS/LABA fixed combination. The UMEC/VI cohort had a smaller proportion of participants using this combination (n=244, 10.0%).

Theophylline use was uncommon in the UMEC and TIO cohorts (UMEC: n=87, 7.0%; TIO: n=131, 5.3%) and was slightly more frequent in the UMEC/VI cohort (n=235, 9.6%).

About half (n=2913, 47.3%) of the participants in the study received “Other” COPD medications prior to their study medication.

Long-term oxygen use

Long-term oxygen use was similar across the cohorts. Among the 5622 participants with available data on long-term oxygen usage in the past 12 months, 155 (2.8%) participants used oxygen <12 hours/day, 47 (0.8%) used oxygen for ≥12 hours/day but not long-term oxygen therapy (LTOT), and 39 (0.7%) received LTOT.

## Table 6 Baseline medications and therapies – FAS

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | Total (N=6165) n (%) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| **Prior COPD Medications (last 12 months)** | | | | | | |
| No COPD Medications, n (%) | 493 (39.6) | 1072 (43.8) | 816 (33.0) | 2381 (38.6) | 0.14 | 0.22 |
| LAMA (other than tiotropium, UMEC) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.05 |
| Yes, n (%) | 5 (0.4) | 11 (0.4) | 4 (0.2) | 20 (0.3) | | |
| No, n (%) | 1241 (99.6) | 2437 (99.6) | 2467 (99.8) | 6145 (99.7) | | |
| LAMA (tiotropium) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.03 |
| Yes, n (%) | 3 (0.2) | 12 (0.5) | 7 (0.3) | 22 (0.4) | | |
| No, n (%) | 1243 (99.8) | 2436 (99.5) | 2464 (99.7) | 6143 (99.6) | | |
| LAMA (UMEC) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.03 |
| Yes, n (%) | 0 (0.0) | 1 (<0.1) | 3 (0.1) | 4 (<0.1) | | |
| No, n (%) | 1246 (100) | 2447 (100) | 2468 (99.9) | 6161 (99.9) | | |
| LABA | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.16 |
| Yes, n (%) | 177 (14.2) | 515 (21.0) | 367 (14.9) | 1059 (17.2) | | |
| No, n (%) | 1069 (85.8) | 1933 (79.0) | 2104 (85.1) | 5106 (82.8) | | |
| LAMA/LABA fixed combination (other than UMEC/VI) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.03 |
| Yes, n (%) | 7 (0.6) | 12 (0.5) | 7 (0.3) | 26 (0.4) | | |
| No, n (%) | 1239 (99.4) | 2436 (99.5) | 2464 (99.7) | 6139 (99.6) | | |
| LAMA/LABA fixed combination (UMEC/VI) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.02 |
| Yes, n (%) | 1 (<0.1) | 3 (0.1) | 5 (0.2) | 9 (0.1) | | |
| No, n (%) | 1245 (99.9) | 2445 (99.9) | 2466 (99.8) | 6156 (99.9) | | |
| ICS | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.10 | 0.01 |
| Yes, n (%) | 114 (9.1) | 292 (11.9) | 304 (12.3) | 710 (11.5) | | |
| No, n (%) | 1132 (90.9) | 2156 (88.1) | 2167 (87.7) | 5455 (88.5) | | |
| ICS/LABA fixed combination | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.41 |
| Yes, n (%) | 292 (23.4) | 244 (10.0) | 625 (25.3) | 1161 (18.8) | | |
| No, n (%) | 954 (76.6) | 2204 (90.0) | 1846 (74.7) | 5004 (81.2) | | |
| Roflumilast (Daliresp®, Daxas®) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.11 | 0.04 |
| Yes, n (%) | 7 (0.6) | 2 (<0.1) | 0 (0.0) | 9 (0.1) | | |
| No, n (%) | 1239 (99.4) | 2446 (99.9) | 2471 (100) | 6156 (99.9) | | |
| Theophyllines | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.07 | 0.16 |
| Yes, n (%) | 87 (7.0) | 235 (9.6) | 131 (5.3) | 453 (7.3) | | |
| No, n (%) | 1159 (93.0) | 2213 (90.4) | 2340 (94.7) | 5712 (92.7) | | |
| Other | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.10 | 0.17 |
| Yes, n (%) | 580 (46.5) | 1060 (43.3) | 1273 (51.5) | 2913 (47.3) | | |
| No, n (%) | 666 (53.5) | 1388 (56.7) | 1199 (48.5) | 3252 (52.7) | | |

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | Total (N=6165) n (%) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| **Long-term oxygen use, past 12 months** | | | | | | |
| n | 1139 | 2174 | 2309 | 5622 | 0.06 | 0.02 |
| Never, n (%) | 1002 (88.0) | 1990 (91.5) | 2112 (91.5) | 5104 (90.8) | | |
| <12 hrs/day, n (%) | 41 (3.6) | 52 (2.4) | 62 (2.7) | 155 (2.8) | | |
| ≥12 hrs/day but not LTOT, n (%) | 9 (0.8) | 24 (1.1) | 14 (0.6) | 47 (0.8) | | |
| LTOT, n (%) | 7 (0.6) | 15 (0.7) | 17 (0.7) | 39 (0.7) | | |
| Unknown, n (%) | 80 (7.0) | 93 (4.3) | 104 (4.5) | 277 (4.9) | | |
| **Other medications and therapies (Last 12 months)** | | | | | | |
| Lipid Lowering Agents | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.09 |
| Yes | 422 (33.9) | 761 (31.1) | 878 (35.5) | 2061 (33.4) | | |
| No | 824 (66.1) | 1687 (68.9) | 1593 (64.5) | 4104 (66.6) | | |
| ACE Inhibitors | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.01 |
| Yes | 311 (25.0) | 631 (25.8) | 627 (25.4) | 1569 (25.5) | | |
| No | 935 (75.0) | 1817 (74.2) | 1844 (74.6) | 4596 (74.5) | | |
| Angiotensin II Receptor Antagonists (ARBs) | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.07 | 0.05 |
| Yes | 184 (14.8) | 377 (15.4) | 426 (17.2) | 987 (16.0) | | |
| No | 1062 (85.2) | 2071 (84.6) | 2045 (82.8) | 5178 (84.0) | | |
| Anti-anginals | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.13 |
| Yes | 500 (40.1) | 1093 (44.6) | 940 (38.0) | 2533 (41.1) | | |
| No | 746 (59.9) | 1355 (55.4) | 1531 (62.0) | 3632 (58.9) | | |
| Anti-arrhythmics | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | <0.01 |
| Yes | 35 (2.8) | 58 (2.4) | 58 (2.3) | 151 (2.4) | | |
| No | 1211 (97.2) | 2390 (97.6) | 2413 (97.7) | 6014 (97.6) | | |
| Anti-coagulants | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.01 |
| Yes | 393 (31.5) | 774 (31.6) | 794 (32.1) | 1961 (31.8) | | |
| No | 853 (68.5) | 1674 (68.4) | 1677 (67.9) | 4204 (68.2) | | |
| Anti-platelets | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.02 |
| Yes | 311 (25.0) | 605 (24.7) | 632 (25.6) | 1548 (25.1) | | |
| No | 935 (75.0) | 1843 (75.3) | 1839 (74.4) | 4617 (74.9) | | |
| Beta Blockers | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.06 | 0.16 |
| Yes | 354 (28.4) | 798 (32.6) | 631 (25.5) | 1783 (28.9) | | |
| No | 892 (71.6) | 1650 (67.4) | 1840 (74.5) | 4382 (71.1) | | |
| Calcium Channel Blockers | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | <0.01 | 0.03 |
| Yes | 221 (17.7) | 467 (19.1) | 441 (17.8) | 1129 (18.3) | | |
| No | 1025 (82.3) | 1981 (80.9) | 2030 (82.2) | 5036 (81.7) | | |
| Digitalis | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.01 |
| Yes | 22 (1.8) | 31 (1.3) | 28 (1.1) | 81 (1.3) | | |
| No | 1224 (98.2) | 2417 (98.7) | 2443 (98.9) | 6084 (98.7) | | |

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | Total (N=6165) n (%) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/VI vs TIO |
|---|---|---|---|---|---|---|
| Diuretics | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.02 |
| Yes | 261 (20.9) | 560 (22.9) | 540 (21.9) | 1361 (22.1) | | |
| No | 985 (79.1) | 1888 (77.1) | 1931 (78.1) | 4804 (77.9) | | |
| Insulin | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.06 | 0.01 |
| Yes | 32 (2.6) | 86 (3.5) | 90 (3.6) | 208 (3.4) | | |
| No | 1214 (97.4) | 2362 (96.5) | 2381 (96.4) | 5957 (96.6) | | |
| Oral antidiabetics | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.14 | 0.06 |
| Yes | 121 (9.7) | 301 (12.3) | 352 (14.2) | 774 (12.6) | | |
| No | 1125 (90.3) | 2147 (87.7) | 2119 (85.8) | 5391 (87.4) | | |
| Systemic Exposure to Glucocorticosteroids | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.11 | 0.08 |
| Yes | 216 (17.3) | 449 (18.3) | 534 (21.6) | 1199 (19.4) | | |
| No | 1030 (82.7) | 1999 (81.7) | 1937 (78.4) | 4966 (80.6) | | |
| Antidepressants | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.16 | 0.19 |
| Yes | 128 (10.3) | 229 (9.4) | 385 (15.6) | 742 (12.0) | | |
| No | 1118 (89.7) | 2219 (90.6) | 2086 (84.4) | 5423 (88.0) | | |
| Glaucoma Medications | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.01 |
| Yes | 42 (3.4) | 61 (2.5) | 67 (2.7) | 170 (2.8) | | |
| No | 1204 (96.6) | 2387 (97.5) | 2404 (97.3) | 5995 (97.2) | | |
| Cytostatics with Cardiovascular Damage Potential | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.04 |
| Yes | 17 (1.4) | 32 (1.3) | 44 (1.8) | 93 (1.5) | | |
| No | 1229 (98.6) | 2416 (98.7) | 2427 (98.2) | 6072 (98.5) | | |

ACE: Angiotensin-converting enzyme; COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroids; FAS: Full analysis set; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; LTOT: Long-term oxygen therapy; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Notes: Percentages based on the number of non-missing responses (n).
1 Std diff was the standardized difference between those exposed to UMEC vs. Tiotropium or those exposed to UMEC/VI vs. Tiotropium. The standardized difference was the raw difference between groups divided by the standard deviation of the specific measure in the Tiotropium group. Additional details are contained in the SAP.
Reference TABLES AND FIGURES: Table 5.0

### 10.2.3. Baseline medical history

Cardiovascular and cerebrovascular medical history

History of heart failure, MI, stroke, and hypertension was similar across all cohorts (see Table 7). A total of 430 (7.0%) participants had a history of heart failure. Among those participants with known type of heart failure, the TIO cohort reported a higher proportion of left-sided heart failure (n=79, 54.1%) in comparison to both the UMEC (n=20, 26.7%) and UMEC/VI (n=54, 25.8%) cohorts. A total of 469 (7.6%) participants had a history of MI, and a prior stroke (all types) was reported by 232 (3.8%) participants. Few participants reported multiple prior events. Over half (n=3508, 56.9%) of participants had current hypertension.

The history of hospitalization for angina, TIA, cardiac arrest, and tachycardia, was similar across cohorts. History of hospitalization for angina was reported among a small proportion of participants (n=264, 4.3%), with most participants hospitalized once (n=176, 3.0%). History of TIA was reported for 159 (2.6%) of participants, where most participants experienced 1 TIA event (n=130, 2.2%). History of atrial fibrillation or flutter (AF) and history of left bundle branch block (LBBB) was slightly more common the UMEC/VI cohorts with 5.5% and 1.1% of participants having a history of AF and LBBB at baseline, respectively.

Other significant respiratory conditions and history of asthma

History of asthma was similar between participants in the UMEC and TIO cohorts with 102 (8.2%) and 285 (11.5%) participants with asthma at enrollment in the study, respectively, and 51 (4.1%) and 120 (4.9%) participants with a history of asthma, respectively. Participants in the UMEC/VI cohort had a smaller proportion of participants with asthma at enrollment (n=99, 4.0%) and a larger proportion of participants with a history of asthma (n=133, 5.4%).

**Table 7 Baseline medical history – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| **History of Diabetes** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.07 | 0.12 |
| Current, n (%) | 181 (14.5) | 441 (18.0) | 488 (19.7) | 1110 (18.0) | | |
| Past, n (%) | 2 (0.2) | 5 (0.2) | 4 (0.2) | 11 (0.2) | | |
| No Medical History, n (%) | 996 (79.9) | 1696 (69.3) | 1864 (75.4) | 4556 (73.9) | | |
| Not assessed, n (%) | 67 (5.4) | 306 (12.5) | 115 (4.7) | 488 (7.9) | | |
| **History of Hypertension** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.05 | 0.09 |
| Current, n (%) | 665 (53.4) | 1450 (59.2) | 1393 (56.4) | 3508 (56.9) | | |
| Past, n (%) | 28 (2.2) | 49 (2.0) | 43 (1.7) | 120 (1.9) | | |
| No Medical History, n (%) | 516 (41.4) | 821 (33.5) | 983 (39.8) | 2320 (37.6) | | |
| Not assessed, n (%) | 37 (3.0) | 128 (5.2) | 52 (2.1) | 217 (3.5) | | |
| **History of MI** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.02 |
| Yes, n (%) | 104 (8.3) | 193 (7.9) | 172 (7.0) | 469 (7.6) | | |
| No, n (%) | 1117 (89.6) | 2198 (89.8) | 2241 (90.7) | 5556 (90.1) | | |
| Unknown, n (%) | 25 (2.0) | 57 (2.3) | 58 (2.3) | 140 (2.3) | | |
| **Number of MI events** | | | | | | |
| n | 1221 | 2391 | 2413 | 6025 | 0.03 | 0.02 |
| 0, n (%) | 1117 (91.5) | 2198 (91.9) | 2241 (92.9) | 5556 (92.2) | | |
| 1, n (%) | 88 (7.2) | 167 (7.0) | 141 (5.8) | 396 (6.6) | | |
| 2, n (%) | 7 (0.6) | 18 (0.8) | 18 (0.7) | 43 (0.7) | | |
| 3+, n (%) | 2 (0.2) | 2 (<0.1) | 3 (0.1) | 7 (0.1) | | |
| Unknown | 7 (0.6) | 6 (0.3) | 10 (0.4) | 23 (0.4) | | |
| **History of Hospitalization for Angina** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.05 |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| Yes, n (%) | 49 (3.9) | 121 (4.9) | 94 (3.8) | 264 (4.3) | | |
| No, n (%) | 1150 (92.3) | 2236 (91.3) | 2299 (93.0) | 5685 (92.2) | | |
| Unknown, n (%) | 47 (3.8) | 91 (3.7) | 78 (3.2) | 216 (3.5) | | |
| **Number of Hospitalizations for Angina** | | | | | | |
| n | 1199 | 2357 | 2393 | 5949 | 0.04 | 0.04 |
| 0, n (%) | 1150 (95.9) | 2236 (94.9) | 2299 (96.1) | 5685 (95.6) | | |
| 1, n (%) | 33 (2.8) | 77 (3.3) | 66 (2.8) | 176 (3.0) | | |
| 2, n (%) | 10 (0.8) | 21 (0.9) | 4 (0.2) | 35 (0.6) | | |
| 3+, n (%) | 1 (<0.1) | 10 (0.4) | 8 (0.3) | 19 (0.3) | | |
| Unknown, n (%) | 5 (0.4) | 13 (0.6) | 16 (0.7) | 34 (0.6) | | |
| **History of Stroke (all types)** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.01 |
| Yes, n (%) | 51 (4.1) | 88 (3.6) | 93 (3.8) | 232 (3.8) | | |
| No, n (%) | 1180 (94.7) | 2314 (94.5) | 2333 (94.4) | 5827 (94.5) | | |
| Unknown, n (%) | 15 (1.2) | 46 (1.9) | 45 (1.8) | 106 (1.7) | | |
| **Number of Strokes (all types)** | | | | | | |
| n | 1231 | 2402 | 2426 | 6059 | 0.03 | 0.01 |
| 0, n (%) | 1180 (95.9) | 2314 (96.3) | 2333 (96.2) | 5827 (96.2) | | |
| 1, n (%) | 47 (3.8) | 75 (3.1) | 79 (3.3) | 201 (3.3) | | |
| 2, n (%) | 3 (0.2) | 7 (0.3) | 8 (0.3) | 18 (0.3) | | |
| 3+, n (%) | 0 (0.0) | 1 (<0.1) | 2 (<0.1) | 3 (<0.1) | | |
| Unknown, n (%) | 1 (<0.1) | 5 (0.2) | 4 (0.2) | 10 (0.2) | | |
| **History of TIA** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.01 |
| Yes, n (%) | 32 (2.6) | 60 (2.5) | 67 (2.7) | 159 (2.6) | | |
| No, n (%) | 1191 (95.6) | 2328 (95.1) | 2347 (95.0) | 5866 (95.2) | | |
| Unknown | 23 (1.8) | 60 (2.5) | 57 (2.3) | 140 (2.3) | | |
| **Number of TIA events** | | | | | | |
| n | 1223 | 2388 | 2414 | 6025 | 0.02 | 0.02 |
| 0, n (%) | 1191 (97.4) | 2328 (97.5) | 2347 (97.2) | 5866 (97.4) | | |
| 1, n (%) | 25 (2.0) | 52 (2.2) | 53 (2.2) | 130 (2.2) | | |
| 2, n (%) | 3 (0.2) | 2 (<0.1) | 7 (0.3) | 12 (0.2) | | |
| 3+, n (%) | 2 (0.2) | 2 (<0.1) | 1 (<0.1) | 5 (<0.1) | | |
| Unknown, n (%) | 2 (0.2) | 4 (0.2) | 6 (0.2) | 12 (0.2) | | |
| **History of Heart Failure** | | | | | | |
| n | 1246 | 2448 | 2470 | 6164 | 0.01 | 0.07 |
| Yes, n (%) | 75 (6.0) | 209 (8.5) | 146 (5.9) | 430 (7.0) | | |
| No, n (%) | 1140 (91.5) | 2177 (88.9) | 2269 (91.9) | 5586 (90.6) | | |
| Unknown, n (%) | 31 (2.5) | 62 (2.5) | 55 (2.2) | 148 (2.4) | | |
| If Yes: | | | | | | |
| Left, n (%) | 20 (26.7) | 54 (25.8) | 79 (54.1) | 153 (35.6) | 0.33 | 0.34 |
| Right, n (%) | 15 (20.0) | 17 (8.1) | 12 (8.2) | 44 (10.2) | | |
| Both, n (%) | 9 (12.0) | 55 (26.3) | 9 (6.2) | 73 (17.0) | | |
| Unknown, n (%) | 31 (41.3) | 83 (39.7) | 46 (31.5) | 160 (37.2) | | |
| **History of Cardiac Arrest** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.01 |
| Yes, n (%) | 10 (0.8) | 13 (0.5) | 14 (0.6) | 37 (0.6) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| No, n (%) | 1211 (97.2) | 2371 (96.9) | 2400 (97.1) | 5982 (97.0) | | |
| Unknown, n (%) | 25 (2.0) | 64 (2.6) | 57 (2.3) | 146 (2.4) | | |
| **Number of Cardiac Arrest events** | | | | | | |
| n | 1221 | 2384 | 2414 | 6019 | 0.03 | 0.02 |
| 0, n (%) | 1211 (99.2) | 2371 (99.5) | 2400 (99.4) | 5982 (99.4) | | |
| 1, n (%) | 6 (0.5) | 9 (0.4) | 13 (0.5) | 28 (0.5) | | |
| 2, n (%) | 1 (<0.1) | 1 (<0.1) | 1 (<0.1) | 3 (<0.1) | | |
| 3+, n (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | | |
| Unknown, n (%) | 3 (0.2) | 3 (0.1) | 0 (0.0) | 6 (<0.1) | | |
| **History of Tachycardia** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.08 |
| Current, n (%) | 17 (1.4) | 26 (1.1) | 39 (1.6) | 82 (1.3) | | |
| Atrial, n (%) | 9 (0.7) | 13 (0.5) | 18 (0.7) | 40 (0.6) | | |
| Ventricular, n (%) | 3 (0.2) | 3 (0.1) | 5 (0.2) | 11 (0.2) | | |
| Unknown, n (%) | 5 (0.4) | 10 (0.4) | 16 (0.6) | 31 (0.5) | | |
| Past, n (%) | 38 (3.0) | 73 (3.0) | 73 (3.0) | 184 (3.0) | | |
| Atrial, n (%) | 17 (1.4) | 41 (1.7) | 26 (1.1) | 84 (1.4) | | |
| Ventricular, n (%) | 6 (0.5) | 7 (0.3) | 17 (0.7) | 30 (0.5) | | |
| Unknown, n (%) | 15 (1.2) | 25 (1.0) | 30 (1.2) | 70 (1.1) | | |
| No Medical History, n (%) | 1127 (90.4) | 2030 (82.9) | 2239 (90.6) | 5396 (87.5) | | |
| Not Assessed, n (%) | 64 (5.1) | 319 (13.0) | 120 (4.9) | 503 (8.2) | | |
| **History of Pathological Brady arrhythmias** | | | | | | |
| n | 1246 | 2447 | 2471 | 6164 | 0.04 | 0.15 |
| Current, n (%) | 2 (0.2) | 15 (0.6) | 20 (0.8) | 37 (0.6) | | |
| Current Pacemaker use | | | | | | |
| Yes, n (%) | 1 (50.0) | 8 (53.3) | 12 (60.0) | 21 (56.8) | | |
| No, n (%) | 1 (50.0) | 6 (40.0) | 7 (35.0) | 14 (37.8) | | |
| Unknown, n (%) | 0 (0.0) | 1 (6.7) | 1 (5.0) | 2 (5.4) | | |
| Past, n (%) | 6 (0.5) | 17 (0.7) | 20 (0.8) | 43 (0.7) | | |
| Past Pacemaker use | | | | | | |
| Yes, n (%) | 2 (33.3) | 10 (58.8) | 12 (60.0) | 24 (55.8) | | |
| No, n (%) | 4 (66.7) | 7 (41.2) | 5 (25.0) | 16 (37.2) | | |
| Unknown, n (%) | 0 (0.0) | 0 (0.0) | 3 (15.0) | 3 (7.0) | | |
| No Medical History, n (%) | 1167 (93.7) | 2081 (85.0) | 2304 (93.2) | 5552 (90.1) | | |
| Not Assessed, n (%) | 71 (5.7) | 334 (13.6) | 127 (5.1) | 532 (8.6) | | |
| **History of Atrial Fibrillation or Flutter** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.16 |
| Current, n (%) | 65 (5.2) | 134 (5.5) | 121 (4.9) | 320 (5.2) | | |
| Past, n (%) | 38 (3.0) | 80 (3.3) | 50 (2.0) | 168 (2.7) | | |
| No Medical History, n (%) | 1076 (86.4) | 1932 (78.9) | 2184 (88.4) | 5192 (84.2) | | |
| Not Assessed, n (%) | 67 (5.4) | 302 (12.3) | 116 (4.7) | 485 (7.9) | | |
| **History of Left Bundle Branch Block** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.16 |
| Current, n (%) | 10 (0.8) | 27 (1.1) | 19 (0.8) | 56 (0.9) | | |
| Past, n (%) | 1 (<0.1) | 5 (0.2) | 3 (0.1) | 9 (0.1) | | |
| No Medical History, n (%) | 1136 (91.2) | 2060 (84.2) | 2300 (93.1) | 5496 (89.1) | | |
| Not Assessed, n (%) | 99 (7.9) | 356 (14.5) | 149 (6.0) | 604 (9.8) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| **History of PCI** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.01 |
| Yes, n (%) | 67 (5.4) | 136 (5.6) | 125 (5.1) | 328 (5.3) | | |
| No, n (%) | 1135 (91.1) | 2233 (91.2) | 2266 (91.7) | 5634 (91.4) | | |
| Unknown, n (%) | 44 (3.5) | 79 (3.2) | 80 (3.2) | 203 (3.3) | | |
| **Number of PCIs** | | | | | | |
| n | 1202 | 2369 | 2391 | 5962 | 0.03 | 0.02 |
| 0, n (%) | 1135 (94.4) | 2233 (94.3) | 2266 (94.8) | 5634 (94.5) | | |
| 1, n (%) | 53 (4.4) | 93 (3.9) | 95 (4.0) | 241 (4.0) | | |
| 2, n (%) | 6 (0.5) | 22 (0.9) | 20 (0.8) | 48 (0.8) | | |
| 3+, n (%) | 4 (0.3) | 11 (0.5) | 6 (0.3) | 21 (0.4) | | |
| Unknown | 4 (0.3) | 10 (0.4) | 4 (0.2) | 18 (0.3) | | |
| **History of CABG** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.01 | 0.02 |
| Yes, n (%) | 33 (2.6) | 74 (3.0) | 68 (2.8) | 175 (2.8) | | |
| No, n (%) | 1181 (94.8) | 2312 (94.4) | 2345 (94.9) | 5838 (94.7) | | |
| Unknown, n (%) | 32 (2.6) | 62 (2.5) | 58 (2.3) | 152 (2.5) | | |
| **History of Peripheral Arterial Revascularization** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.08 | 0.04 |
| Yes, n (%) | 40 (3.2) | 54 (2.2) | 31 (1.3) | 125 (2.0) | | |
| No, n (%) | 1170 (93.9) | 2319 (94.7) | 2358 (95.4) | 5847 (94.8) | | |
| Unknown, n (%) | 36 (2.9) | 75 (3.1) | 82 (3.3) | 193 (3.1) | | |
| **History of Carotid Surgery or Stenting** | | | | | | |
| N | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.01 |
| Yes, n (%) | 37 (3.0) | 62 (2.5) | 59 (2.4) | 158 (2.6) | | |
| No, n (%) | 1177 (94.5) | 2316 (94.6) | 2340 (94.7) | 5833 (94.6) | | |
| Unknown, n (%) | 32 (2.6) | 70 (2.9) | 72 (2.9) | 174 (2.8) | | |
| **History of Other Cardiovascular Diagnosis/Procedure** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.01 |
| Yes, n (%) | 96 (7.7) | 212 (8.7) | 220 (8.9) | 528 (8.6) | | |
| No, n (%) | 1111 (89.2) | 2150 (87.8) | 2164 (87.6) | 5425 (88.0) | | |
| Unknown, n (%) | 39 (3.1) | 86 (3.5) | 87 (3.5) | 212 (3.4) | | |
| **History of Hyperlipidemia** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.04 | 0.09 |
| Current, n (%) | 331 (26.6) | 633 (25.9) | 728 (29.5) | 1692 (27.4) | | |
| Past, n (%) | 55 (4.4) | 132 (5.4) | 108 (4.4) | 295 (4.8) | | |
| No Medical History, n (%) | 746 (59.9) | 1360 (55.6) | 1442 (58.4) | 3548 (57.6) | | |
| Not Assessed, n (%) | 114 (9.1) | 323 (13.2) | 193 (7.8) | 630 (10.2) | | |
| **History of Hypertriglyceridemia** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.10 | 0.09 |
| Current, n (%) | 114 (9.1) | 211 (8.6) | 345 (14.0) | 670 (10.9) | | |
| Past, n (%) | 27 (2.2) | 99 (4.0) | 84 (3.4) | 210 (3.4) | | |
| No Medical History, n (%) | 947 (76.0) | 1748 (71.4) | 1780 (72.0) | 4475 (72.6) | | |
| Not Assessed, n (%) | 158 (12.7) | 390 (15.9) | 262 (10.6) | 810 (13.1) | | |
| **History of Asthma** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.07 | 0.15 |
| Current, n (%) | 102 (8.2) | 99 (4.0) | 285 (11.5) | 486 (7.9) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| Past, n (%) | 51 (4.1) | 133 (5.4) | 120 (4.9) | 304 (4.9) | | |
| No Medical History, n (%) | 1030 (82.7) | 1936 (79.1) | 1973 (79.8) | 4939 (80.1) | | |
| Not Assessed, n (%) | 63 (5.1) | 280 (11.4) | 93 (3.8) | 436 (7.1) | | |
| **History of GORD** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.08 | 0.15 |
| Current, n (%) | 160 (12.8) | 313 (12.8) | 445 (18.0) | 918 (14.9) | | |
| Past, n (%) | 34 (2.7) | 78 (3.2) | 53 (2.1) | 165 (2.7) | | |
| No Medical History, n (%) | 986 (79.1) | 1750 (71.5) | 1861 (75.3) | 4597 (74.6) | | |
| Not Assessed, n (%) | 66 (5.3) | 307 (12.5) | 112 (4.5) | 485 (7.9) | | |
| **History of Other Significant Respiratory Conditions** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.09 | 0.05 |
| Yes, n (%) | 80 (6.4) | 210 (8.6) | 251 (10.2) | 541 (8.8) | | |
| No, n (%) | 1126 (90.4) | 2150 (87.8) | 2161 (87.5) | 5437 (88.2) | | |
| Unknown, n (%) | 40 (3.2) | 88 (3.6) | 59 (2.4) | 187 (3.0) | | |
| **History of Significant Benign Tumor** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.07 | 0.04 |
| Yes, n (%) | 66 (5.3) | 81 (3.3) | 97 (3.9) | 244 (4.0) | | |
| No, n (%) | 1139 (91.4) | 2278 (93.1) | 2313 (93.6) | 5730 (92.9) | | |
| Unknown, n (%) | 41 (3.3) | 89 (3.6) | 61 (2.5) | 191 (3.1) | | |
| **History of Lung Cancer/Other Malignant Cancer** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.02 | 0.13 |
| Current, n (%) | 22 (1.8) | 50 (2.0) | 53 (2.1) | 125 (2.0) | | |
| Past, n (%) | 91 (7.3) | 173 (7.1) | 172 (7.0) | 436 (7.1) | | |
| No Medical History, n (%) | 1082 (86.8) | 1932 (78.9) | 2152 (87.1) | 5166 (83.8) | | |
| Not Assessed, n (%) | 51 (4.1) | 293 (12.0) | 94 (3.8) | 438 (7.1) | | |
| **History of Chronic Kidney Disease** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.04 |
| Yes, n (%) | 68 (5.5) | 124 (5.1) | 161 (6.5) | 353 (5.7) | | |
| No, n (%) | 1138 (91.3) | 2233 (91.2) | 2233 (90.4) | 5604 (90.9) | | |
| Unknown, n (%) | 40 (3.2) | 91 (3.7) | 77 (3.1) | 208 (3.4) | | |
| **History of Glaucoma** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.03 | 0.15 |
| Current, n (%) | 26 (2.1) | 55 (2.2) | 69 (2.8) | 150 (2.4) | | |
| Past, n (%) | 6 (0.5) | 17 (0.7) | 21 (0.8) | 44 (0.7) | | |
| No Medical History, n (%) | 1150 (92.3) | 2049 (83.7) | 2267 (91.7) | 5466 (88.7) | | |
| Not Assessed, n (%) | 64 (5.1) | 327 (13.4) | 114 (4.6) | 505 (8.2) | | |
| **History of Depression/Other Psychiatric Disorders** | | | | | | |
| n | 1246 | 2448 | 2471 | 6165 | 0.13 | 0.17 |
| Current, n (%) | 123 (9.9) | 254 (10.4) | 455 (18.4) | 832 (13.5) | | |
| Past, n (%) | 43 (3.5) | 54 (2.2) | 100 (4.0) | 197 (3.2) | | |
| No Medical History, n (%) | 1027 (82.4) | 1827 (74.6) | 1823 (73.8) | 4677 (75.9) | | |
| Not Assessed, n (%) | 53 (4.3) | 313 (12.8) | 93 (3.8) | 459 (7.4) | | |
| **Family History of Cardiovascular and Cerebrovascular Disease in a First-Degree Female Relative Diagnosed <60 Years of Age** | | | | | | |
| **n** | 1246 | 2448 | 2471 | 6165 | 0.17 | 0.09 |
| **Yes** | 31 (2.5) | 83 (3.4) | 84 (3.4) | 198 (3.2) | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) | Std Diff[1] UMEC vs TIO | Std Diff[1] UMEC/ VI vs TIO |
|---|---|---|---|---|---|---|
| **Yes, but Age Unknown at Diagnosis** | 22 (1.8) | 49 (2.0) | 80 (3.2) | 151 (2.4) | | |
| **No** | 706 (56.7) | 1524 (62.3) | 1676 (67.8) | 3906 (63.4) | | |
| **Unknown** | 487 (39.1) | 792 (32.4) | 631 (25.5) | 1910 (31.0) | | |
| **Family History of Cardiovascular and Cerebrovascular Disease in a First-Degree Male Relative Diagnosed <55 Years of Age** | | | | | | |
| **n** | 1246 | 2448 | 2471 | 6165 | 0.16 | 0.08 |
| **Yes** | 43 (3.5) | 118 (4.8) | 123 (5.0) | 284 (4.6) | | |
| **Yes, but Age Unknown at Diagnosis** | 41 (3.3) | 72 (2.9) | 93 (3.8) | 206 (3.3) | | |
| **No** | 668 (53.6) | 1459 (59.6) | 1614 (65.3) | 3741 (60.7) | | |
| **Unknown** | 494 (39.6) | 799 (32.6) | 641 (25.9) | 1934 (31.4) | | |

CABG: Coronary Artery Bypass Grafting; FAS: Full analysis set; GORD: Gastro-Oesophageal Reflux Disease; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; SAP: Statistical analysis plan; TIA: transient ischemic attack; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Std diff was the standardized difference between those exposed to UMEC vs. Tiotropium or those exposed to UMEC/VI vs. Tiotropium. The standardized difference was the raw difference between groups divided by the standard deviation of the specific measure in the Tiotropium group. Additional details are contained in the SAP.
Notes: Percentages based on the number of non-missing responses (n).
Reference TABLES AND FIGURES: Table 6.0

### 10.2.4. Study treatment exposure

First study medication switch and first add-on COPD medication

Among participants in the UMEC cohort, the most common (first) medication switch was to UMEC/VI (n=162, 13.0%), followed by switching to ICS+LABA (n=106, 8.5%), then ICS+LAMA (n=72, 5.8%) (see Table 8). Two (0.2%) participants switched to roflumilast. The most common first add-on COPD medication in the UMEC cohort was ICS+LABA (n=65, 5.2%).

Among the UMEC/VI cohort, the most common first medication switch was to ICS+LABA (n=193, 7.9%), followed by switching to LAMA+LABA other than UMEC/VI (n=147, 6.0%), then ICS+LAMA (n=130, 5.3%). The most common first add-on COPD medication in the UMEC/VI cohort was ICS (n=168, 6.9%).

Among the TIO cohort, the most common first medication switch was to LABA+LAMA other than UMEC/VI (n=178, 7.2%), followed by switching to ICS+LABA (n=128, 5.2%), then ICS+LAMA (n=77, 3.1%). The most common first add-on COPD medication in the TIO cohort was ICS+LABA (n=157, 6.4%).

**Table 8 First study medication switch and first add-on COPD medication – FAS**

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) |
|---|---|---|---|
| **First Medications Switch to[1]** | | | |

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) |
|---|---|---|---|
| UMEC | NA | 20 (0.8) | 25 (1.0) |
| UMEC/VI | 162 (13.0) | NA | 63 (2.5) |
| Tiotropium (TIO) | 49 (3.9) | 38 (1.6) | NA |
| ICS | 17 (1.4) | 43 (1.8) | 28 (1.1) |
| LAMA other than Tio, UMEC | 7 (0.6) | 6 (0.2) | 12 (0.5) |
| LABA | 14 (1.1) | 60 (2.5) | 17 (0.7) |
| LAMA+LABA other than UMEC/VI | 52 (4.2) | 147 (6.0) | 178 (7.2) |
| ICS+LAMA | 72 (5.8) | 130 (5.3) | 77 (3.1) |
| ICS+LABA | 106 (8.5) | 193 (7.9) | 128 (5.2) |
| Other | 2 (0.2) | 1 (<0.1) | 0 (0.0) |
| **First Add-on COPD Medications[2]** | | | |
| ICS | 43 (3.5) | 168 (6.9) | 110 (4.5) |
| LABA | 23 (1.8) | 0 (0.0) | 58 (2.3) |
| ICS+LABA | 65 (5.2) | 54 (2.2) | 157 (6.4) |
| Roflumilast | 0 (0.0) | 3 (0.1) | 4 (0.2) |

COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Study medication switch was defined as starting one or several different COPD maintenance therapy(ies) within 30 days before or after the discontinuation date of the study medication. A participant could contribute to several categories.
2 Study medication augmentation with add-on COPD medication was defined as taking one different COPD maintenance therapy with new treatment starting ≥1 day after the exposure index date and ≥31 days before the discontinuation date of the study medication. A participant could contribute to one category only.
Note: All percentages based on N in column heading.
Participants switching from initial study medication also used other COPD medications in addition to those listed.
Reference TABLES AND FIGURES: Table 10.0

Duration of exposure to study medication

Study medication was discontinued by almost half (n=613, 49.2%) of the participants in the UMEC cohort (see Table 9). Less participants discontinued in the UMEC/VI cohort (n=904, 36.9%), and TIO cohort (n=864, 35.0%). The median (Q1-Q3) duration of exposure to the study medication was shortest among participants in the UMEC cohort with 945.5 (380.0, 1512.0) days, followed by the UMEC/VI cohort at 1105.0 (546.5, 1592.5) days, then the TIO cohort at 1154.0 (560.0, 1684.0) days.

Study medication switches occurred in 428 (34.3%), 538 (22.0%), and 513 (20.8%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. Among participants with a study medication switch, the median (Q1-Q3) time to first switch was 499.0 (182.0, 904.0) days, 385.0 (118.0, 874.0) days, and 487.0 (187.0, 914.0) days for participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

The proportion of participants that received augmentation with add-on COPD medication was similar across treatment cohorts at about 12-14%. The median (Q1-Q3) time to first add-on COPD medication was 406.0 (159.0, 721.0), 356.0 (148.0, 668.0), and 328.0 (113.0, 673.0) days for participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

Total time on study medication with no add-on medication was 2917.9, 6349.4, and 6530.9 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. The total time on study medication with add-on medication was 324.6, 683.2, and 808.4 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts with add-on medication, respectively.

At 6 months, 1056 (84.8%), 2162 (88.3%), and 2236 (90.5%) of participants were still on study medication (without add-on) across the UMEC, UMEC/VI, and TIO cohorts, respectively. At 12 months, 945 (75.8%), 1986 (81.1%), and 2059 (83.3%) of participants were still on study medication (without add-on) across the UMEC, UMEC/VI, and TIO cohorts, respectively. At 24 months, 740 (59.4%) participants in the UMEC cohort were still on study medication (without add-on), compared to 1685 (68.8%) participants in the UMEC/VI and 1703 (68.9%) participants in the TIO cohort.

**Table 9 Duration of exposure to study medication – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **Study Medication Discontinuation[1]** | | | |
| n | 1246 | 2448 | 2471 |
| Yes, n (%) | 613 (49.2) | 904 (36.9) | 864 (35.0) |
| No, n (%) | 633 (50.8) | 1544 (63.1) | 1607 (65.0) |
| **Duration (days) of Exposure to Study Medication[2]** | | | |
| n | 1246 | 2448 | 2471 |
| Mean (SD) | 950.5 (615.85) | 1049.3 (593.91) | 1084.9 (596.93) |
| Median | 945.5 | 1105.0 | 1154.0 |
| Q1, Q3 | (380.0, 1512.0) | (546.5, 1592.5) | (560.0, 1684.0) |
| Range | (1, 2185) | (1, 1961) | (1, 2238) |
| **Total Participants Time on Study Medication[3]** | | | |
| n | 1246 | 2448 | 2471 |
| Total (Person-years) | 3242.5 | 7032.6 | 7339.3 |
| **Study Medication Switch[4]** | | | |
| n | 1246 | 2448 | 2471 |
| Yes, n (%) | 428 (34.3) | 538 (22.0) | 513 (20.8) |
| No, n (%) | 818 (65.7) | 1910 (78.0) | 1958 (79.2) |
| If Yes, Time (days) to First Study Medication Switch[5] | | | |
| n | 428 | 538 | 513 |
| Mean (SD) | 591.4 (469.18) | 544.4 (489.28) | 591.9 (474.21) |
| Median | 499.0 | 385.0 | 487.0 |
| Q1, Q3 | (182.0, 904.0) | (118.0, 874.0) | (187.0, 914.0) |
| Range | (1, 1826) | (1, 1822) | (1, 1827) |
| **Augmentation with Add-on COPD Medication[6]** | | | |
| n | 1246 | 2448 | 2471 |
| Yes, n (%) | 153 (12.3) | 297 (12.1) | 355 (14.4) |
| No, n (%) | 1093 (87.7) | 2151 (87.9) | 2116 (85.6) |
| If Yes, Time (days) to First Add-on COPD Medication[7] | | | |
| n | 153 | 297 | 355 |

| | **UMEC (N=1246)** | **UMEC/VI (N=2448)** | **TIO (N=2471)** |
|---|---|---|---|
| Mean (SD) | 484.0 (387.30) | 456.9 (387.93) | 450.9 (411.82) |
| Median | 406.0 | 356.0 | 328.0 |
| Q1, Q3 | (159.0, 721.0) | (148.0, 668.0) | (113.0, 673.0) |
| Range | (3, 1556) | (2, 1710) | (2, 1794) |
| **Total Participant Time on Study Medication (No Add-on Medication)** | | | |
| n | 1246 | 2448 | 2471 |
| Total (Person-years) | 2917.9 | 6349.4 | 6530.9 |
| **Total Participant Time on Study Medication with Add-on Medications** | | | |
| n | 1246 | 2448 | 2471 |
| Total (Person-years) | 324.6 | 683.2 | 808.4 |
| **Participants Still on Study Medication (only) at 6 Months of Observation** | | | |
| n (%) | 1056 (84.8) | 2162 (88.3) | 2236 (90.5) |
| **Participants Still on Study Medication plus Add-on COPD Medication at 6 Months of Observation** | | | |
| n (%) | 111 (8.9) | 205 (8.4) | 247 (10.0) |
| **Participants Still on Study Medication (only) at 12 Months of Observation** | | | |
| n (%) | 945 (75.8) | 1986 (81.1) | 2059 (83.3) |
| **Participants Still on Study Medication plus Add-on COPD Medication at 12 Months of Observation** | | | |
| n (%) | 91 (7.3) | 175 (7.1) | 205 (8.3) |
| **Participants Still on Study Medication (only) at 18 Months of Observation** | | | |
| n (%) | 841 (67.5) | 1833 (74.9) | 1870 (75.7) |
| **Participants Still on Study Medication plus Add-on COPD Medication at 18 Months of Observation** | | | |
| n (%) | 77 (6.2) | 141 (5.8) | 173 (7.0) |
| **Participants Still on Study Medication (only) at 24 Months of Observation** | | | |
| n (%) | 740 (59.4) | 1685 (68.8) | 1703 (68.9) |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **Participants Still on Study Medication plus Add-on COPD Medication at 24 Months of Observation** | | | |
| n (%) | 55 (4.4) | 119 (4.9) | 144 (5.8) |

COPD: Chronic obstructive pulmonary disease; FAS: Full analysis set; Q1: First quartile; Q3: Third quartile; SD: standard deviation; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Study medication discontinuation was defined as the cessation of study medication. Discontinuation date was set at 14 days after the end of the final study medication prescription.
2 Duration of Exposure to Study Medication was defined as the time in days from study medication exposure index date to study medication discontinuation date, study discontinuation date, death date, site closure date or study last participant last visit date (31JAN2023), whichever occurred first.
3 Time on study medication, regardless of the concomitant intake of switch treatment or Add-on COPD medication.
4 Study medication switch was defined as starting one or several different COPD maintenance therapy(ies) within 30 days before or after the discontinuation date of the study medication. First switch date was defined as the date of first prescription of the new COPD maintenance therapy.
5 Time to first Study Medication Switch was defined, among participants experiencing a switch, as the time in days from study medication exposure index date to first switch or study medication discontinuation date, whichever occurred first.
6 Study medication augmentation with add-on COPD medication was defined as taking one different COPD maintenance therapy with new treatment starting ≥1 day after the exposure index date and ≥31 days before the discontinuation date of the study medication. The first augmentation date was defined as the prescription date of the first new COPD maintenance therapy.
7 Time to first augmentation was defined among participants experiencing an augmentation, as the time in days from exposure index date to first augmentation date.
Reference TABLES AND FIGURES: Table 11.0

Reason for study medication discontinuation

Among all participants, the most common reasons for study medication discontinuation were physician decision (n=533, 22.4%) and lack of efficacy (n=401, 16.8%) (see Table 10). A similar distribution was observed among participants in the UMEC cohort (physician decision: n=175, 28.5%; lack of efficacy: n=110, 17.9%) and TIO cohort (physician decision: n=212, 24.5%; lack of efficacy: n=131, 15.2%). The UMEC/VI cohort had a smaller proportion of participants discontinuing the study medication due to physician decision (n=146, 16.2%) compared to participants in the UMEC and TIO cohorts. In the UMEC/VI cohort, the most common reasons for study medication discontinuation were lack of efficacy (n=160, 17.7%) and death (n=148, 16.4%).

Other reasons for discontinuation were also reported by 159 (25.9%), 245 (27.1%), and 279 (32.3%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. Additional information regarding the specific reasons can be found in ANNEX 1 – TLFs Listing 3.

**Table 10 Reason for study medication discontinuation – FAS**

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | All Participants (N=6165) n (%) |
|---|---|---|---|---|
| **Participants who Discontinued Study Medication** | 613 (49.2) | 904 (36.9) | 864 (35.0) | 2381 (38.6) |
| Reason for Discontinuation: | | | | |

| | UMEC (N=1246) n (%) | UMEC/VI (N=2448) n (%) | TIO (N=2471) n (%) | All Participants (N=6165) n (%) |
|---|---|---|---|---|
| Adverse Event | 74 (12.1) | 144 (15.9) | 88 (10.2) | 306 (12.9) |
| Lack of Efficacy | 110 (17.9) | 160 (17.7) | 131 (15.2) | 401 (16.8) |
| Lost to Follow-Up | 1 (0.2) | 0 (0.0) | 0 (0.0) | 1 (<0.1) |
| Progressive Disease | 45 (7.3) | 54 (6.0) | 37 (4.3) | 136 (5.7) |
| Physician Decision | 175 (28.5) | 146 (16.2) | 212 (24.5) | 533 (22.4) |
| Withdrew Consent | 3 (0.5) | 2 (0.2) | 3 (0.3) | 8 (0.3) |
| Death | 44 (7.2) | 148 (16.4) | 109 (12.6) | 301 (12.6) |
| Site Closed | 0 (0.0) | 4 (0.4) | 2 (0.2) | 6 (0.3) |
| Study Closed | 1 (0.2) | 0 (0.0) | 3 (0.3) | 4 (0.2) |
| Other | 159 (25.9) | 245 (27.1) | 279 (32.3) | 683 (28.7) |
| Missing | 1 (0.2) | 1 (0.1) | 0 (0.0) | 2 (<0.1) |

FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: Percentages based on N in column heading except for reason for discontinuation based on number who discontinued.
Study medication discontinuation was defined as the cessation of study medication. Participants could continue study medication after discontinuation of the study.
Reference TABLES AND FIGURES: Table 13.0

Augmentation with ICS and/or LABA during observation period

Participants that received augmentation with ICS typically received augmentation within 6 months (about 3% across cohorts) or more than 18 months (about 5% across cohorts) after initiating study medication (ANNEX 1 – TLFs Table 12.0). Similarly, participants that received augmentation with LABA typically received augmentation >0-6 months or >18 months after initiating study medication. Few participants received augmentation with LABA among the UMEC/VI cohort (≤1% at each 6-month interval). After initiating UMEC, 41 (3.3%) participants received augmentation with LABA >18 months. Augmentation with LABA was most common in the TIO cohort with 64 (2.6%) participants receiving LABA within 6 months of TIO initiation, 31 (1.3%) between 6 and 12 months, 22 (0.9%) between 12 and 18 months, and 120 (4.9%) more than 18 months after initiation TIO.

## 10.3. Outcome data

Outcome data are presented in Section 10.4 Main results.

## 10.4. Main results

### 10.4.1. Primary outcomes

#### 10.4.1.1. Non-inferiority of UMEC and UMEC/VI to TIO for risk of the composite endpoint based on an analysis of time to first event

The main analysis of the composite outcome of confirmed MI, stroke, heart failure, or sudden cardiac death demonstrated non-inferiority for UMEC and UMEC/VI compared to TIO (see Table 11).

Among the participants in the FAS, the adjusted HR (95% CI) for the composite outcome (confirmed MI, stroke, heart failure, or sudden cardiac death) during exposure to the study drug was 1.254 (0.830, 1.896) for UMEC vs TIO, and 1.352 (0.952, 1.922) for UMEC/VI vs TIO. As the upper 95% confidence limits were below 2.0 and the lower confidence limits were below 1.0, non-inferiority to TIO can be assumed for both UMEC and UMEC/VI.

Kaplan-Meier survival function for composite endpoints

There are no discernable differences in the survival function for the composite endpoint between the UMEC and TIO, and UMEC/VI and TIO cohorts (see Figure 3).

Sensitivity analyses of composite endpoints

Sensitivity analyses were performed by using the full observation period (i.e., not censored on the end of study treatment exposure as described in Section 9.9.4. The adjusted HR (95% CI) was 0.955 (0.674, 1.354) for UMEC vs TIO, and 1.155 (0.852, 1.566) for UMEC/VI vs TIO (see ANNEX 1 – TLFs Table 20.0.1 and Table 59.0.1).

In sensitivity analyses using the PSM cohorts during the exposure period, similar HR estimates but wider confidence intervals were observed: adjusted HRs (95% CI) were 1.323 (0.811, 2.158) for UMEC vs TIO, and 1.289 (0.852, 1.950) for UMEC/VI vs TIO (see ANNEX 1 – TLFs Table 20.0.2 and Table 59.0.2).

Additional sensitivity analyses were conducted using covariate adjustment (see ANNEX 1 – TLFs Table 20.0.3 and Table 59.0.3), PSM cohort without stabilized IPTW weights and adjusting only for gender, history of diabetes, history of MI, history of stroke, and ethnicity (see ANNEX 1 – TLFs Table 20.0.4 and Table 59.0.4), investigator-reported composite events (see ANNEX 1 – TLFs Table 20.0.5 and Table 59.0.5), censored on positive COVID-19 test/infection date (see ANNEX 1 – TLFs Table 20.0.6 and Table 59.0.6), including sites with quality issues and unsigned casebooks (see ANNEX 1 – TLFs Table 20.0.7 and Table 59.0.7).

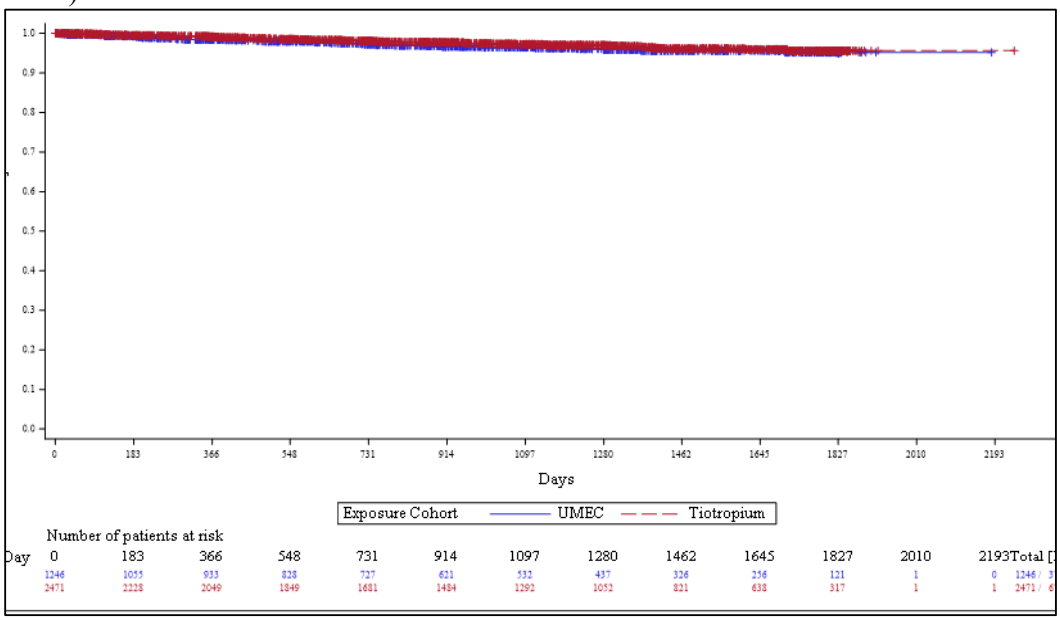
**Table 11 Risk of the composite MI, stroke, heart failure, and sudden cardiac death of UMEC or UMEC/VI compared to TIO during exposure period – FAS**

| Exposure or Contrast | N | n | Events | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|
| UMEC | 1246 | 1236 | 37 | |
| TIO | 2471 | 2458 | 66 | |
| UMEC vs TIO | | | | 1.254 (0.830,1.896) |
| UMEC/VI | 2448 | 2429 | 87 | |
| TIO | 2471 | 2458 | 66 | |
| UMEC/VI vs TIO | | | | 1.352 (0.952,1.922) |

N: total number of participants in each treatment group; n: number per treatment group that are included in the analysis represented by this table; CAT: COPD Assessment Test; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced Expiratory Volume in one Second; FAS: Full analysis set; ICS: Inhaled corticosteroids; IPTW: Inverse Probability of Treatment Weighting; MI: myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: All coefficients were estimated using stabilized IPTW weights. Additional statistical adjustment for confounders for UMEC/VI vs TIO, included country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; history of MI, Stroke, heart failure; ethnicity; physician specialty; ICS use at baseline; and time-varying use of add-on COPD medication. UMEC vs TIO was also adjusted by education.
Reference TABLES AND FIGURES: Table 20.0 and Table 59.0

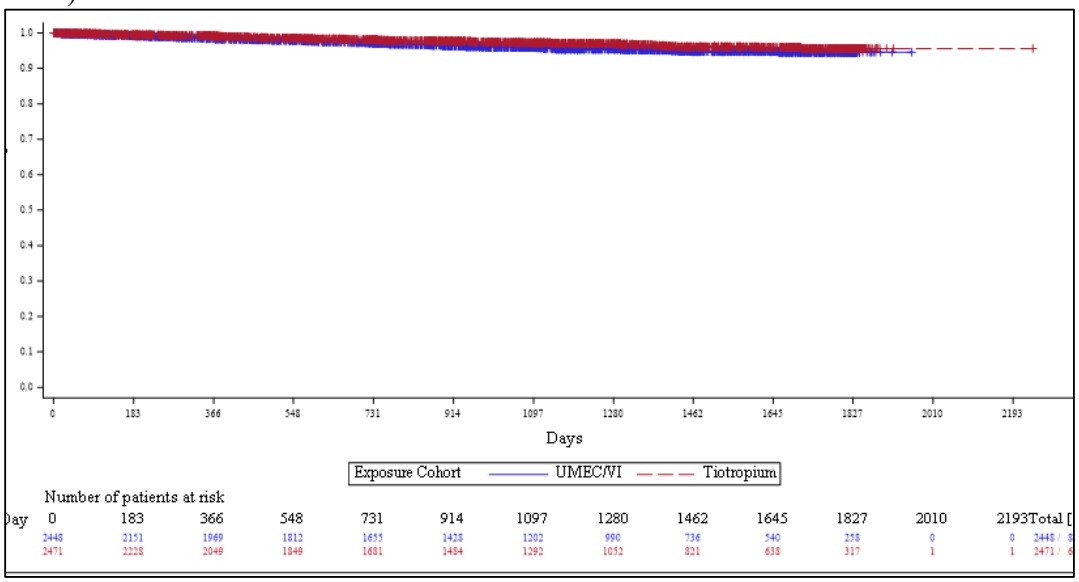
**Figure 3 Kaplan-Meier survival function for composite of confirmed MI, stroke, heart failure, or sudden cardiac death for UMEC or UMEC/VI versus TIO during exposure period – FAS**

A) UMEC versus TIO




FAS: Full analysis set; MI: myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium
[1] Number of participants /number of first events
Reference TABLES AND FIGURES: Table 58.1, Table 58.2, and Figure 13.1

B) UMEC/VI versus TIO




FAS: Full analysis set; MI: myocardial infarction; TIO: Tiotropium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
[1] Number of participants /number of first events
Reference TABLES AND FIGURES: Table 19.1, Table 19.2, and Figure 5.1

### 10.4.1.2. Incidence rate and frequency of the composite endpoint

A composite event (MI, stroke, heart failure, or sudden cardiac death) was observed among 37 (3.0%), 89 (3.6%), and 67 (2.7%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively (see Table 12). The corresponding incidence rates (95% CI) were 1.16 (0.814, 1.594), 1.39 (1.034, 1.584), and 0.92 (0.716, 1.174) events per 100 person-years. The incidence rate in the UMEC/VI cohort was slightly higher compared to the other cohorts.

During the exposure period, 44, 105 and 85 composite events (MI, stroke, heart failure, or sudden cardiac death) occurred among the respective UMEC, UMEC/VI, and TIO cohorts. The event rates (95% CI) were 1.357 (0.986, 1.822), 1.493 (1.221, 1.807), and 1.158 (0.925, 1.432) events per 100 person-years, respectively.

**Table 12 Incidence and event rates of the composite endpoint by cohort during the exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) |
|---|---|---|---|---|
| **Composite Outcome** | | | | |
| **Incidence Rate[1,2]** | | | | |
| n (%) of participants | 37 (3.0) | 89 (3.6) | 67 (2.7) | 193 (3.1) |
| Person-Time (Years) | 3199.1 | 6913.2 | 7250.5 | 17362.8 |
| Rate per 100 Person-Years | 1.157 | 1.287 | 0.924 | 1.112 |
| 95% CI | (0.814, 1.594) | (1.034, 1.584) | (0.716, 1.174) | (0.960, 1.280) |
| **Event Rate[3,4]** | | | | |
| n of events | 44 | 105 | 85 | 234 |
| Person-Time (Years) | 3242.5 | 7032.6 | 7339.3 | 17614.4 |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) |
|---|---|---|---|---|
| per 100 Person-Years | 1.357 | 1.493 | 1.158 | 1.328 |
| 95% CI | (0.986, 1.822) | (1.221, 1.807) | (0.925, 1.432) | (1.164, 1.510) |
| **MI** | | | | |
| n (%) of participant (first events)[2] | 9 (0.7) | 26 (1.1) | 15 (0.6) | 50 (0.8) |
| Total number of events | 9 | 26 | 18 | 53 |
| **Stroke** | | | | |
| n (%) of participants (first events)[2] | 7 (0.6) | 17 (0.7) | 18 (0.7) | 42 (0.7) |
| Total number of events | 7 | 18 | 19 | 44 |
| **Heart Failure** | | | | |
| n (%) of participants (first events)[2] | 18 (1.4) | 24 (1.0) | 26 (1.1) | 68 (1.1) |
| Total number of events | 23 | 36 | 37 | 96 |
| **Sudden Cardiac Death** | | | | |
| n (%) of participant[2] | 5 (0.4) | 25 (1.0) | 11 (0.4) | 41 (0.7) |

CI: Confidence interval; FAS: Full analysis set; MI: Myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Composite outcome was any of confirmed MI, stroke, heart failure, or sudden cardiac death.
2 Percentages were based on the column totals (N). Only the first event of a given type was included in the counts; time after the first event was not included in person-time totals.
3 Composite outcome was any of MI, Stroke, Heart Failure, or Sudden Cardiac Death.
4 Percentages based on the n of events. Multiple events of each type except death were included in counts; person-time reflected the whole Exposure period.Reference TABLES AND FIGURES: Table 16.0 and Table 17.0

Incidence and frequency of composite endpoint by history of COPD exacerbation

*Participants with history of COPD exacerbation in past 12 months*

The incidence rates (95% CI) of a composite event among participants with a history of COPD exacerbations were 2.40 (1.345, 3.964), 1.51 (0.897, 2.392), and 1.23 (0.704, 2.000) events per 100 person-years for the UMEC, UMEC/VI, and TIO cohorts, respectively (see Table 13).

*Participants with no history of COPD exacerbation in past 12 months*

The incidence rates (95% CI) of a composite event among participants with no history of COPD exacerbations were 0.85 (0.535, 1.294), 1.24 (0.969, 1.565), and 0.86 (0.638, 1.127) events per 100 person-years for the UMEC, UMEC/VI, and TIO cohorts, respectively.

**Table 13 Incidence and event rates and ratios for composite of confirmed MI, stroke, heart failure and sudden cardiac death during exposure period in participants with history of COPD exacerbation in past 12 months for UMEC, UMEC/VI, and TIO – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **Participants with history of COPD exacerbation in past 12 months** | 264 | 441 | 469 |
| **Number (%) participants with:** | | | |
| No composite events | 249 (94.3) | 423 (95.9) | 453 (96.6) |
| 1 composite event | 14 (5.3) | 17 (3.9) | 14 (3.0) |
| ≥2 composite events | 1 (0.4) | 1 (0.2) | 2 (0.4) |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 624.1 | 1189.3 | 1299.2 |
| Number of First Events | 15 | 18 | 16 |
| Incidence Rate per 100 Person-Years[2] | 2.40 | 1.51 | 1.23 |
| (95% CI) | (1.345, 3.964) | (0.897, 2.392) | (0.704, 2.000) |
| Incidence Rate Ratio (unadjusted) | 1.95 | 1.23 | reference |
| (95% CI) | (0.965, 3.948) | (0.627, 2.410) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 641.5 | 1214.4 | 1319.6 |
| Total Number of Events | 16 | 19 | 23 |
| Event Rate per 100 Person-Years[3] | 2.49 | 1.56 | 1.74 |
| (95% CI) | (1.426, 4.050) | (0.942, 2.443) | (1.105, 2.615) |
| Event Rate Ratio (unadjusted) | 1.43 | 0.90 | reference |
| (95% CI) | (0.756, 2.709) | (0.489, 1.648) | |
| **Participants with no history of COPD exacerbation in past 12 months** | 982 | 2007 | 2002 |
| **Number (%) participants with:** | | | |
| No composite events | 960 (97.8) | 1936 (96.5) | 1951 (97.5) |
| 1 composite event | 17 (1.7) | 63 (3.1) | 43 (2.1) |
| ≥2 composite events | 5 (0.5) | 8 (0.4) | 8 (0.4) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2575.0 | 5723.9 | 5951.2 |
| Number of First Events | 22 | 71 | 51 |
| Incidence Rate per 100 Person-Years[2] | 0.85 | 1.24 | 0.86 |
| (95% CI) | (0.535, 1.294) | (0.969, 1.565) | (0.638, 1.127) |
| Incidence Rate Ratio (unadjusted) | 1.00 | 1.45 | reference |
| (95% CI) | (0.605, 1.644) | (1.010, 2.074) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 2601.0 | 5818.2 | 6019.7 |
| Total Number of Events | 28 | 86 | 62 |
| Event Rate per 100 Person-Years[3] | 1.08 | 1.48 | 1.03 |
| (95% CI) | (0.715, 1.556) | (1.182, 1.825) | (0.790, 1.320) |
| Event Rate Ratio (unadjusted) | 1.05 | 1.44 | reference |
| (95% CI) | (0.669, 1.633) | (1.035, 1.989) | |

CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; FAS: Full analysis set; MI: myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis.
Reference TABLES AND FIGURES: Table 18.0.2 and Table 57.0.2

### 10.4.2. Secondary outcomes

This study was powered to test for differences between the UMEC or UMEC/VI and TIO cohorts for the primary composite endpoint only. The study was not powered to test for non-inferiority or differences in the secondary endpoints.

#### 10.4.2.1. UMEC or UMEC/VI comparison to TIO for risk of MI, stroke, and heart failure individually based on an analysis of time to first event

Participants in the UMEC/VI cohort showed an increased risk of MI compared to the TIO cohort with adjusted HR of 2.195 (1.053, 4.575). Risk of MI was lower between the UMEC and TIO cohort with adjusted HR (95% CI) of 1.754 (0.748, 4.115) (see Table 14). However low incidence of MI was observed across all 3 treatments. The risk of stroke and heart failure was similar between the UMEC or UMEC/VI and TIO cohorts. The adjusted HR (95% CI) for stroke was 1.096 (0.458, 2.621) for the UMEC vs TIO cohort and 1.018 (0.470, 2.207) for the UMEC/VI vs TIO cohort. The adjusted HR (95% CI) for heart failure was 1.287 (0.654, 2.532) for the UMEC vs TIO and 0.832 (0.459, 1.509) for the UMEC/VI vs TIO cohorts.

**Table 14 Risk of confirmed MI, stroke, and heart failure between UMEC or UMEC/VI compared to TIO during exposure period – FAS**

| Exposure or Contrast | N | n | Events | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|
| **MI** | | | | |
| UMEC | 1246 | 1236 | 9 | |
| TIO | 2471 | 2458 | 15 | |
| UMEC vs TIO | | | | 1.754 (0.748, 4.115) |
| UMEC/VI | 2448 | 2429 | 24 | |
| TIO | 2471 | 2458 | 15 | |
| UMEC/VI vs TIO | | | | 2.195 (1.053, 4.575) |
| **Stroke** | | | | |
| UMEC | 1246 | 1236 | 7 | |
| TIO | 2471 | 2458 | 18 | |
| UMEC vs TIO | | | | 1.096 (0.458, 2.621) |
| UMEC/VI | 2448 | 2429 | 17 | |
| TIO | 2471 | 2458 | 18 | |
| UMEC/VI vs TIO | | | | 1.018 (0.470, 2.207) |
| **Heart failure** | | | | |
| UMEC | 1246 | 1236 | 18 | |
| TIO | 2471 | 2458 | 25 | |
| UMEC vs TIO | | | | 1.287 (0.654, 2.532) |
| UMEC/VI | 2448 | 2429 | 24 | |
| TIO | 2471 | 2458 | 25 | |
| UMEC/VI vs TIO | | | | 0.832 (0.459, 1.509) |

N: total number of participants in each treatment group; n: number per treatment group that are included in the analysis represented by this table; CAT: COPD Assessment Test; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced Expiratory Volume in one Second; FAS: Full analysis set; ICS: inhaled corticosteroids; IPTW: Inverse Probability of Treatment Weighting; MI: Myocardial Infraction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.

Notes:

All coefficients were estimated using stabilized IPTW weights. Additional statistical adjustment for confounders included country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; history of the event (MI, stroke, heart failure); ethnicity; physician specialty; ICS use at baseline; and time-varying use of add-on COPD medication. UMEC vs TIO also adjusted for education.

Reference TABLES AND FIGURES: Table 24.0, Table 27.0, Table 30.0, Table 63.0, Table 66.0, and Table 69.0

#### 10.4.2.2. Incidence rate and frequency of MI, stroke, and heart failure

MI

MI was observed among 9 (0.7%), 26 (1.1%), and 15 (0.6%) participants in the respective UMEC, UMEC/VI, and TIO cohorts (see Table 15). A low incidence of MI was observed across all cohorts with rates ranging between 0.21 (0.115, 0.338) per 100 person-years in the TIO cohort and 0.37 (0.243, 0.546) per 100 person-years in the UMEC/VI cohort.

Stroke

Stroke was observed among 7 (0.6%), 17 (0.7%), and 18 (0.7%) participants in the UMEC UMEC/VI and TIO cohorts, respectively. Low incidence of stroke was observed across all cohorts. The rates (95% CI) were similar between cohorts with rates of 0.22 (0.087, 0.446), 0.24 (0.141, 0.388), and 0.25 (0.146, 0.389) per 100 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

Heart failure

Heart failure was observed among 18 (1.4%), 24 (1.0%), and 26 (1.1%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. Low incidence of heart failure was observed across all cohorts. The UMEC cohort had a slightly higher incidence (incidence rate [95% CI]=0.56 [0.332, 0.884]) than the UMEC/VI (incidence rate [95% CI]=0.34 [0.220, 0.511]) and TIO cohorts (incidence rate [95% CI]=0.36 [0.233, 0.522]).

**Table 15 Incidence and event rates for confirmed MI, stroke, and heart failure for UMEC, UMEC/VI, and TIO during exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **MI** | | | |
| **Number (%) Participants with:** | | | |
| No events | 1237 (99.3) | 2422 (98.9) | 2456 (99.4) |
| 1 event | 9 (0.7) | 26 (1.1) | 14 (0.6) |
| ≥2 events | 0 (0.0) | 0 (0.0) | 1 (<0.1) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 3229.9 | 6980.6 | 7310.7 |
| Number of First Events | 9 (0.7) | 26 (1.1) | 15 (0.6) |
| Incidence Rate per 100 Person-Years[2] | 0.28 | 0.37 | 0.21 |
| (95% CI) | (0.127, 0.529) | (0.243, 0.546) | (0.115, 0.338) |
| Incidence Rate Ratio (unadjusted) | 1.36 | 1.82 | reference |
| (95% CI) | (0.594, 3.103) | (0.962, 3.427) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 9 | 26 | 18 |
| Event Rate per 100 Person-Years[3] | 0.28 | 0.37 | 0.25 |
| (95% CI) | (0.127, 0.527) | (0.242, 0.542) | (0.145, 0.388) |
| Event Rate Ratio (unadjusted) | 1.13 | 1.51 | reference |
| (95% CI) | (0.508, 2.519) | (0.827, 2.749) | |
| **Stroke** | | | |
| **Number (%) of Participants with:** | | | |
| No events | 1239 (99.4) | 2431 (99.3) | 2453 (99.3) |
| 1 event | 7 (0.6) | 16 (0.7) | 17 (0.7) |
| ≥2 events | 0 (0.0%) | 1 (<0.1) | 1 (<0.1) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 3234.2 | 7012.0 | 7313.8 |
| Number of First Events | 7 (0.6) | 17 (0.7) | 18 (0.7) |
| Incidence Rate per 100 Person-Years[2] | 0.22 | 0.24 | 0.25 |
| (95% CI) | (0.087, 0.446) | (0.141, 0.388) | (0.146, 0.389) |
| Incidence Rate Ratio (unadjusted) | 0.88 | 0.99 | reference |
| (95% CI) | (0.367, 2.105) | (0.508, 1.911) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 7 | 18 | 19 |
| Event Rate per 100 Person-Years[3] | 0.22 | 0.26 | 0.26 |
| (95% CI) | (0.087, 0.445) | (0.152, 0.405) | (0.156, 0.404) |
| Event Rate Ratio (unadjusted) | 0.83 | 0.99 | reference |
| (95% CI) | (0.351, 1.984) | (0.519, 1.884) | |
| **Heart failure** | | | |
| **Number (%) of Participants with:** | | | |
| No events | 1228 (98.6) | 2424 (99.0) | 2445 (98.9) |
| 1 event | 14 (1.1) | 18 (0.7) | 18 (0.7) |
| ≥2 events | 4 (0.3) | 6 (0.2) | 8 (0.3) |
| **Incidence Rate** | | | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 3217.4 | 6984.2 | 7301.9 |
| Number of First Events | 18 (1.4) | 24 (1.0) | 26 (1.1) |
| Incidence Rate per 100 Person-Years[2] | 0.56 | 0.34 | 0.36 |
| (95% CI) | (0.332, 0.884) | (0.220, 0.511) | (0.233, 0.522) |
| Incidence Rate Ratio (unadjusted) | 1.57 | 0.97 | reference |
| (95% CI) | (0.861, 2.866) | (0.554, 1.681) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 23 | 36 | 37 |
| Event Rate per 100 Person-Years[3] | 0.71 | 0.51 | 0.50 |
| (95% CI) | (0.450, 1.064) | (0.359, 0.709) | (0.355, 0.695) |
| Event Rate Ratio (unadjusted) | 1.41 | 1.02 | reference |
| (95% CI) | (0.836, 2.368) | (0.642, 1.607) | |

CI: confidence interval; FAS: Full analysis set; MI: myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis Reference TABLES AND FIGURES: Table 17.0, Table 22.0, Table 25.0, Table 28.0, Table 61.0, Table 64.0, and Table 67.0

#### 10.4.2.3. Incidence rate and frequency of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)

In the UMEC PSM cohort, 29 (2.6%) participants had 1 serious pneumonia/serious LRTI event and 8 (0.7%) had ≥2 events (see Table 16). Similarly, in the TIO PSM cohort, 31 (2.8%) participants had 1 serious pneumonia/serious LRTI event and 3 (0.3%) participants that had ≥2 events. The incidence rates (95% CI) of serious pneumonia/serious LRTI were 1.29 (0.906, 1.773), and 1.05 (0.725, 1.462) per 100 person-years among the UMEC and TIO PSM cohorts, respectively.

In the UMEC/VI PSM cohort, 60 (4.3%) participants had 1 serious pneumonia/serious LRTI event. In the TIO PSM cohort, 39 (2.8%) participants had 1 serious pneumonia/serious LRTI event. The incidence rates (95% CI) of serious pneumonia/serious LRTI were 1.79 (1.401, 2.255), and 1.10 (0.796, 1.471) events per 100 person-years among the UMEC/VI and TIO PSM cohorts, respectively.

**Table 16 Incidence rates and event rates for serious pneumonia/serious LRTI (composite endpoint) UMEC or UMEC/VI versus TIO during exposure period – PSM cohorts**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| Number (%) of Participants with: | | |
| No events | 1077 (96.7) | 1080 (96.9) |
| 1 event | 29 (2.6) | 31 (2.8) |
| ≥2 events | 8 (0.7) | 3 (0.3) |
| **Incidence Rate** | | |

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2875.9 | 3249.0 |
| Number of First Events | 37 | 34 |
| Incidence Rate per 100 Person-Years[2] | 1.29 | 1.05 |
| (95% CI) | (0.906, 1.773) | (0.725, 1.462) |
| Incidence Rate Ratio | 1.23 | reference |
| (95% CI) | (0.772, 1.959) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 2922.0 | 3292.5 |
| Total Number of Events | 46 | 38 |
| Event Rate per 100 Person-Years[3] | 1.57 | 1.15 |
| (95% CI) | (1.153, 2.100) | (0.817, 1.584) |
| Event Rate Ratio | 1.36 | reference |
| (95% CI) | (0.888, 2.096) | |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| Number (%) of Participants with: | | |
| No events | 1332 (94.9) | 1360 (96.9) |
| 1 event | 60 (4.3) | 39 (2.8) |
| ≥2 events | 12 (0.9) | 5 (0.4) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 4021.4 | 4016.2 |
| Number of First Events | 72 | 44 |
| Incidence Rate per 100 Person-Years[2] | 1.79 | 1.10 |
| (95% CI) | (1.401, 2.255) | (0.796, 1.471) |
| Incidence Rate Ratio | 1.63 | reference |
| (95% CI) | (1.12, 2.38) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 4117.3 | 4073.9 |
| Total Number of Events | 87 | 50 |
| Event Rate per 100 Person-Years[3] | 2.11 | 1.23 |
| (95% CI) | (1.692, 2.606) | (0.911, 1.618) |
| Event Rate Ratio | 1.72 | reference |
| (95% CI) | (1.22, 2.44) | |

CI: Confidence interval; LRTI: Lower Respiratory Tract Infection; PSM: Propensity Score Matched; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 31.0.1 and Table 70.0.1

Hazard ratio of serious pneumonia/ serious lower respiratory tract infection (LRTI) (composite endpoint)

The adjusted HR (95% CI) for the risk of serious pneumonia/ serious LRTI was 1.185 (0.820, 1.713) for the UMEC vs TIO cohorts and was 1.328 (0.989, 1.783) for the UMEC/VI vs TIO cohorts (see Table 17).

**Table 17 Risk of serious pneumonia/serious LRTI (composite endpoint) for UMEC, UMEC/VI compared to TIO during exposure period – FAS**

| Exposure or Contrast | N | n | Events | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|
| UMEC | 1246 | 1236 | 42 | |
| TIO | 2471 | 2458 | 84 | |
| UMEC vs TIO | | | | 1.185 (0.820, 1.713) |
| UMEC/VI | 2448 | 2429 | 119 | |
| TIO | 2471 | 2458 | 84 | |
| UMEC/VI vs TIO | | | | 1.328 (0.989, 1.783) |

N: total number of participants in each treatment group; n: number per treatment group that are included in the analysis represented by this table; CAT: COPD Assessment Test; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; FAS: Full analysis set; $FEV_1$: Forced Expiratory Volume in one Second; ICS: inhaled corticosteroids; IPTW: Inverse Probability of Treatment Weighting; LRTI: Lower Respiratory Tract Infection; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: All coefficients were estimated using stabilized IPTW weights. Additional statistical adjustment for confounders for UMEC/VI vs TIO, included country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; ICS use at baseline; time varying use of add-on COPD medication; ethnicity; physician specialty; history of COPD exacerbation; and history of pneumonia/LRTI prior to enrolment.
UMEC vs TIO was also adjusted by education.
Reference TABLES AND FIGURES: Table 32.0 and Table 71.0

### 10.4.2.4. Overall, CV-related, and non-CV-related mortality rates

Mortality rates by cohort during the exposure period

During the exposure period, 291 deaths occurred, with 41 (3.3%), 143 (5.8%), and 107 (4.3%) deaths among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively (see Table 18). The mortality rates (95% CI) were 1.264 (0.907, 1.715), 2.033 (1.714, 2.395), and 1.458 (1.195, 1.762) deaths per 100 person-years among the UMEC, UMEC/VI, and TIO cohorts, respectively.

A low number of sudden cardiac deaths were observed in study. There were 5 (0.4%), 25 (1.0%), and 11 (0.4%) participants that had sudden cardiac deaths in the UMEC, UMEC/VI, and TIO cohorts, respectively. The mortality rates (95% CI) of sudden cardiac death were notably low with 0.154 (0.050, 0.360), 0.355 (0.230, 0.525), and 0.150 (0.075, 0.268) per 100 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

Non-sudden CV deaths occurred among 7 (0.6%), 40 (1.6%), and 29 (1.2%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. The mortality rates (95% CI) were 0.216 (0.087, 0.445), 0.569 (0.406, 0.775), 0.395 (0.265, 0.567) per 100 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

Most deaths were non-CV: 29 (2.3%), 78 (3.2%), and 67 (2.7%) non-CV deaths occurred in the UMEC, UMEC/VI, and TIO cohorts, respectively. The mortality rate (95% CI) was 0.894 (0.599, 1.284), 1.109 (0.877, 1.384), 0.913 (0.707, 1.159) non-CV deaths per 100 person-years among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively.

**Table 18 Mortality rates by cohort during the exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) | Total (N=6165) |
|---|---|---|---|---|
| **All Deaths** | | | | |
| n of Events (%) | 41 (3.3) | 143 (5.8) | 107 (4.3) | 291 (4.7) |
| Person-Time (Years) | 3242.5 | 7032.6 | 7339.3 | 17614.4 |
| Rate per 100 Person-Years | 1.264 | 2.033 | 1.458 | 1.652 |
| 95% CI | (0.907, 1.715) | (1.714, 2.395) | (1.195, 1.762) | (1.468, 1.853) |
| **Sudden Cardiac Death** | | | | |
| n of Events (%) | 5 (0.4) | 25 (1.0) | 11 (0.4) | 41 (0.7) |
| Person-Time (Years) | 3242.5 | 7032.6 | 7339.3 | 17614.4 |
| Rate per 100 Person-Years | 0.154 | 0.355 | 0.150 | 0.233 |
| 95% CI | (0.050, 0.360) | (0.230, 0.525) | (0.075, 0.268) | (0.167, 0.316) |
| **Cardiovascular Death, Non-Sudden** | | | | |
| n of Events (%) | 7 (0.6) | 40 (1.6) | 29 (1.2) | 76 (1.2) |
| Person-Time (Years) | 3242.5 | 7032.6 | 7339.3 | 17614.4 |
| Rate per 100 Person-Years | 0.216 | 0.569 | 0.395 | 0.431 |
| 95% CI | (0.087, 0.445) | (0.406, 0.775) | (0.265, 0.567) | (0.340, 0.540) |
| **Non-Cardiovascular Death** | | | | |
| n of Events (%) | 29 (2.3) | 78 (3.2) | 67 (2.7) | 174 (2.8) |
| Person-Time (Years) | 3242.5 | 7032.6 | 7339.3 | 17614.4 |
| Rate per 100 Person-Years | 0.894 | 1.109 | 0.913 | 0.988 |
| 95% CI | (0.599, 1.284) | (0.877, 1.384) | (0.707, 1.159) | (0.846, 1.146) |

CI: Confidence interval; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Multiple events of each type except death were included in counts; person-time reflects the whole Exposure period.
Reference TABLES AND FIGURES: Table 16.0, Table 17.0

Mortality rates by cohort during the observation period

During the observation period, 82 (6.6%), 214 (8.7%), and 167 (6.8%) deaths occurred among participants in the UMEC, UMEC/VI, and TIO cohorts, respectively. The overall mortality rates (95% CI) were 1.845 (1.468, 2.291), 2.561 (2.229, 2.928), and 1.912 (1.633, 2.225) deaths per 100 person-years for UMEC, UMEC/VI, and TIO cohorts respectively (see Table 19).

CV-related deaths occurred among 24 (1.9%), 89 (3.6%), and 58 (2.3%) participants in the UMEC, UMEC/VI, and TIO cohorts during the observation period, respectively. The CV-related mortality rates (95% CI) were 0.540 (0.346, 0.804), 1.065 (0.855, 1.311), and 0.664 (0.504, 0.859) per 100 person-years for the UMEC, UMEC/VI, and TIO cohorts, respectively.

Non-CV-related deaths occurred among 58 (4.7%), 125 (5.1%), and 109 (4.4%) participants in the UMEC, UMEC/VI, and TIO cohorts during the observation period, respectively. Non-CV-related mortality rates (95% CI) were 1.305 (0.991, 1.687), 1.496 (1.245, 1.782), and 1.248 (1.025, 1.506) per 100 person-years for UMEC, UMEC/VI, and TIO cohorts, respectively.

**Table 19 Overall, CV-related, and non-CV-related mortality rates for UMEC, UMEC/VI, and TIO during observation period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| **Overall Mortality Rates** | | | |
| Person-Time (Years) | 4443.3 | 8356.8 | 8732.6 |
| Deaths, n (%) | 82 (6.6) | 214 (8.7) | 167 (6.8) |
| Mortality Rate per 100 Person-Years | 1.845 | 2.561 | 1.912 |
| (95% CI) | (1.468, 2.291) | (2.229, 2.928) | (1.633, 2.225) |
| **CV-related Mortality Rates** | | | |
| Person-Time (Years) | 4443.3 | 8356.8 | 8732.6 |
| Deaths, n (%) | 24 (1.9) | 89 (3.6) | 58 (2.3) |
| Mortality Rate per 100 Person-Years | 0.540 | 1.065 | 0.664 |
| (95% CI) | (0.346, 0.804) | (0.855, 1.311) | (0.504, 0.859) |
| **Non-CV-related Mortality Rates** | | | |
| Person-Time (Years) | 4443.3 | 8356.8 | 8732.6 |
| Deaths, n (%) | 58 (4.7) | 125 (5.1) | 109 (4.4) |
| Mortality Rate per 100 Person-Years | 1.305 | 1.496 | 1.248 |
| (95% CI) | (0.991, 1.687) | (1.245, 1.782) | (1.025, 1.506) |

CI: Confidence interval; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
The full observation period was included in the person-time total.
Reference TABLES AND FIGURES: Table 33.0.1, Table 34.0.1, Table 35.0.1, Table 72.0.1, Table 73.0.1, and Table 74.0.1

## 10.4.3. Safety outcomes

### 10.4.3.1. Incidence and frequency of stroke (all types)

The incidence rates of stroke (all types) in the UMEC and TIO PSM cohorts were similar (see Table 20). In each cohort 7 (0.6%) participants had a stroke and the incidence rates (95% CI) were 0.24 (0.097, 0.495) and 0.21 (0.086, 0.439) events per 100 person-years among participants in the UMEC and TIO PSM cohorts, respectively.

The incidence rates of stroke (all types) in the UMEC/VI and TIO PSM cohorts were similar. At least 1 stroke occurred among 10 and 12 participants in the UMEC/VI and TIO PSM cohorts. The incidence rates (95% CI) were 0.24 (0.117, 0.448) and 0.30 (0.153, 0.517) events per 100 person-years among participants in the UMEC/VI and TIO PSM cohorts, respectively.

**Table 20 Incidence rates and event rates for stroke (all types) for UMEC or UMEC/VI versus TIO during exposure period – PSM cohorts**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| Number (%) of participants with: | | |
| No events | 1107 (99.4) | 1107 (99.4) |
| 1 event | 7 (0.6) | 7 (0.6) |
| ≥2 events | 0 (0.0) | 0 (0.0) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2913.8 | 3285.3 |

| | | |
|---|---|---|
| Number of First Events | 7 | 7 |
| Incidence Rate per 100 Person-Years[2] | 0.24 | 0.21 |
| (95% CI) | (0.097, 0.495) | (0.086, 0.439) |
| Incidence Rate Ratio | 1.13 | reference |
| (95% CI) | (0.395, 3.214) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 2922.0 | 3292.5 |
| Total Number of Events | 7 | 7 |
| Event Rate per 100 Person-Years[3] | 0.24 | 0.21 |
| (95% CI) | (0.096, 0.494) | (0.085, 0.438) |
| Event Rate Ratio | 1.13 | reference |
| (95% CI) | (0.395, 3.212) | |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| Number (%) of participants with: | | |
| No events | 1394 (99.3) | 1392 (99.1) |
| 1 event | 9 (0.6) | 11 (0.8) |
| ≥2 events | 1 (<0.1) | 1 (<0.1) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 4102.6 | 4058.0 |
| Number of First Events | 10 | 12 |
| Incidence Rate per 100 Person-Years[2] | 0.24 | 0.30 |
| (95% CI) | (0.117, 0.448) | (0.153, 0.517) |
| Incidence Rate Ratio | 0.82 | reference |
| (95% CI) | (0.356, 1.908) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 4117.3 | 4073.9 |
| Total Number of Events | 11 | 13 |
| Event Rate per 100 Person-Years[3] | 0.27 | 0.32 |
| (95% CI) | (0.133, 0.478) | (0.170, 0.546) |
| Event Rate Ratio | 0.84 | reference |
| (95% CI) | (0.375, 1.869) | |

CI: Confidence interval; PSM: Propensity score matched; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
There was one stroke event with undetermined type.
Note for UMEC vs TIO: The 95% Confidence Intervals were calculated assuming a Poisson distribution.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 36.0 and Table 75.0

#### 10.4.3.2. Incidence rate and frequency of hospitalization for heart failure

Hospitalization for heart failure was uncommon in the study population and occurred in ≤2.0% of participants in the UMEC and TIO PSM cohorts during the exposure period (see Table 21). At least 1 hospitalization for heart failure occurred among 22 participants in the UMEC and 17 in the TIO PSM cohorts during the exposure period. The incidence rates (95% CI) of hospitalization for heart failure were 0.86 (0.540, 1.305), and 0.59 (0.343, 0.942) per 100 person-years among the UMEC and TIO PSM cohorts, respectively.

Similarly, few hospitalizations for heart failure were observed for both the UMEC/VI and TIO PSM cohorts during the exposure period. At least 1 hospitalization for heart failure occurred among 31 participants in the UMEC/VI and 26 participants in the TIO PSM cohort during the exposure period. The incidence rates (95% CI) of hospitalization for heart failure were 0.87 (0.588, 1.229), and 0.72 (0.470, 1.053) per 100 person-years among the UMEC/VI and TIO PSM cohorts, respectively.

**Table 21 Incidence rates and event rates for hospitalization for heart failure for UMEC or UMEC/VI versus TIO during exposure period – PSM cohorts**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| Number (%) of Participants with: | | |
| No events | 1092 (98.0) | 1097 (98.5) |
| 1 event | 18 (1.6) | 10 (0.9) |
| ≥2 events | 4 (0.4) | 7 (0.6) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2552.7 | 2889.5 |
| Number of First Events | 22 | 17 |
| Incidence Rate per 100 Person-Years[2] | 0.86 | 0.59 |
| (95% CI) | (0.540, 1.305) | (0.343, 0.942) |
| Incidence Rate Ratio | 1.46 | reference |
| (95% CI) | (0.778, 2.759) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 2922.0 | 3292.5 |
| Total Number of Events | 27 | 25 |
| Event Rate per 100 Person-Years[3] | 0.92 | 0.76 |
| (95% CI) | (0.609, 1.344) | (0.491, 1.121) |
| Event Rate Ratio | 1.22 | reference |
| (95% CI) | (0.706, 2.097) | |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| Number (%) Participants with: | | |
| No events | 1373 (97.8) | 1378 (98.1) |
| 1 event | 27 (1.9) | 17 (1.2) |
| ≥2 events | 4 (0.3) | 9 (0.6) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event1 | 3580.7 | 3616.7 |
| Number of First Events | 31 | 26 |
| Incidence Rate per 100 Person-Years[2] | 0.87 | 0.72 |
| (95% CI) | (0.588, 1.229) | (0.470, 1.053) |
| Incidence Rate Ratio | 1.20 | reference |
| (95% CI) | (0.715, 2.028) | |
| **Event Rate** | | |

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| Sum of Person-Time (Years) Exposure Period | 4117.3 | 4073.9 |
| Total Number of Events | 40 | 36 |
| Event Rate per 100 Person-Years[3] | 0.97 | 0.88 |
| (95% CI) | (0.694, 1.323) | (0.619, 1.223) |
| Event Rate Ratio | 1.10 | reference |
| (95% CI) | (0.701, 1.725) | |

CI: Confidence interval; PSM: Propensity score matched; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 39.0 and Table 78.0

### 10.4.3.3. Incidence rate and frequency of reported serious adverse events (SAEs) and drug-related adverse events (AEs)

Incidence rates and frequency of reported SAEs

SAEs were observed among 254 (20.4%), 609 (24.9%), and 499 (20.2%) participants in the respective UMEC, UMEC/VI and TIO cohorts (see Table 22). Most participants had one event with 152 (12.2%), 340 (13.9%), and 296 (12.0%) participants in the UMEC, UMEC/VI, and TIO cohorts respectively, and multiple SAEs were reported among 102 (8.2%), 269 (11.0%), and 203 (8.2%) participants in the respective cohorts. The incidence rate (95% CI) was highest in the UMEC/VI cohort at 10.05 (9.266, 10.879), followed by the UMEC cohort at 9.05 (7.973, 10.236), then the TIO cohort at 7.61 (6.961, 8.313) SAEs per 100 person-years.

**Table 22 Incidence rates and event rates for Serious Adverse Events for UMEC, UMEC/VI, and TIO during exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Number (%) Participants with: | | | |
| No events | 992 (79.6%) | 1839 (75.1) | 1972 (79.8%) |
| 1 event | 152 (12.2%) | 340 (13.9) | 296 (12.0%) |
| ≥2 events | 102 (8.2%) | 269 (11.0) | 203 (8.2%) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2806.1 | 6060.9 | 6552.9 |
| Number of First Events | 254 | 609 | 499 |
| Incidence Rate per 100 Person-Years[2] | 9.05 | 10.05 | 7.61 |
| (95% CI) | (7.973, 10.236) | (9.266, 10.879) | (6.961, 8.313) |
| Incidence Rate Ratio (unadjusted) | 1.19 | 1.32 | reference |
| (95% CI) | (1.022, 1.383) | (1.172, 1.485) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 470 | 1159 | 932 |
| Event Rate per 100 Person-Years[3] | 14.50 | 16.48 | 12.70 |
| (95% CI) | (13.214, 15.867) | (15.545, 17.457) | (11.896, 13.541) |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Event Rate Ratio (unadjusted) | 1.14 | 1.30 | reference |
| (95% CI) | (1.022, 1.275) | (1.191, 1.415) | |

CI: Confidence interval; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in person-time for incidence but was counted for event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis.
Reference TABLES AND FIGURES: Table 40.0 and Table 79.0

Incidence rates and frequency of reported drug-related AEs

Drug-related AEs were similar across the cohorts with 58 (4.7%), 85 (3.5%), and 62 (2.5%) participants in the respective UMEC, UMEC/VI and TIO cohorts (see Table 23). One event was observed in 42 (3.4%), 66 (2.7%), and 51 (2.1%) participants in the UMEC, UMEC/VI, and TIO cohort, respectively. The incidence rate (95% CI) for drug-related AEs was highest in the UMEC cohort at 2.07 (1.569, 2.672), followed by the UMEC/VI cohort at 1.40 (1.120, 1.734), then the TIO cohort at 0.95 (0.725, 1.213) drug-related AEs per 100 person-years.

**Table 23 Incidence rates and event rates for drug-related Adverse Events for UMEC, UMEC/VI versus TIO during exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Number (%) of participants with: | | | |
| No events | 1188 (95.3) | 2363 (96.5) | 2409 (97.5) |
| 1 event | 42 (3.4) | 66 (2.7) | 51 (2.1) |
| ≥2 events | 16 (1.3) | 19 (0.8) | 11 (0.4%) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2806.1 | 6060.9 | 6552.9 |
| Number of First Events | 58 | 85 | 62 |
| Incidence Rate per 100 Person-Years[2] | 2.07 | 1.40 | 0.95 |
| (95% CI) | (1.569, 2.672) | (1.120, 1.734) | (0.725, 1.213) |
| Incidence Rate Ratio (unadjusted) | 2.18 | 1.48 | reference |
| (95% CI) | (1.527, 3.125) | (1.068, 2.056) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 77 | 116 | 76 |
| Event Rate per 100 Person-Years[3] | 2.37 | 1.65 | 1.04 |
| (95% CI) | (1.874, 2.968) | (1.363, 1.978) | (0.816, 1.296) |
| Event Rate Ratio (unadjusted) | 2.29 | 1.59 | reference |
| (95% CI) | (1.670, 3.148) | (1.193, 2.127) | |

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|

CI: Confidence interval; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis.
Reference TABLES AND FIGURES: Table 41.0 and Table 80.0

#### 10.4.3.4. Incidence rate and frequency of serious cardiovascular events of special interests

Frequency of serious cardiovascular and cerebrovascular adverse events of special interests

Similar proportions of participants who experienced cardiovascular AESIs were observed across all cohorts (see Table 24). Among participants in the UMEC cohort, 132 (10.6%) participants experienced 177 cardiovascular AESIs. In the UMEC/VI cohort, 288 (11.8%) participants had 393 cardiovascular AESIs. Participants in the TIO cohort had 352 cardiovascular AESIs among 250 (10.1%) participants.

Specifically, 42 cardiac arrhythmias occurred among 38 (3.0%) participants in the UMEC cohort, 113 cardiac arrhythmias occurred among 93 (3.8%) participants in the UMEC/VI cohort, and 110 cardiac arrhythmias occurred among 100 (4.0%) participants in the TIO cohort.

Additionally, 46 cardiac failures were reported among 36 (2.9%) participants in the UMEC cohort, 109 cardiac failures among 85 (3.5%) participants in the UMEC/VI cohort, and 86 cardiac failures among 64 (2.6%) participants in the TIO cohort.

Among participants in the UMEC cohort, 13 (1.0%) participants experienced 14 cerebrovascular AESIs. The same proportion of participants were observed in the UMEC/VI and TIO cohorts with 40 cerebrovascular AESIs in 37 (1.5%) participants and 43 events in 38 (1.5%) participants, respectively.

**Table 24 Cardiovascular and cerebrovascular Adverse Events of Special Interest (AESI) during exposure period – FAS**

| | UMEC (N=1246) Total Events, Number of Participants, n (%) | UMEC/VI (N=2448) Total Events, Number of Participants, n (%) | TIO (N=2471) Total Events, Number of Participants, n (%) | Total (N=6165) Total Events, Number of Participants, n (%) |
|---|---|---|---|---|
| Any Cardiovascular AESI | 177, 132 (10.6) | 393, 288 (11.8) | 352, 250 (10.1) | 922, 670 (10.9) |
| Cardiac Arrhythmias | 42, 38 (3.0) | 113, 93 (3.8) | 110, 100 (4.0) | 265, 231 (3.7) |
| Cardiac Ischemia | 37, 33 (2.6) | 81, 70 (2.9) | 59, 49 (2.0) | 177, 152 (2.5) |
| Cardiac Failure | 46, 36 (2.9) | 109, 85 (3.5) | 86, 64 (2.6) | 241, 185 (3.0) |
| Hypertension (new Diagnosis or Escalated Treatment) | 38, 37 (3.0) | 51, 48 (2.0) | 54, 50 (2.0) | 143, 135 (2.2) |

| | UMEC (N=1246) Total Events, Number of Participants, n (%) | UMEC/VI (N=2448) Total Events, Number of Participants, n (%) | TIO (N=2471) Total Events, Number of Participants, n (%) | Total (N=6165) Total Events, Number of Participants, n (%) |
|---|---|---|---|---|
| Stroke | 14, 13 (1.0) | 39, 36 (1.5) | 43, 38 (1.5) | 96, 87 (1.4) |
| Any Cerebrovascular AESI | 14, 13 (1.0) | 40, 37 (1.5) | 43, 38 (1.5) | 97, 88 (1.4) |

AESI: Adverse Event of Special Interest; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Stroke was included in both the Cardiovascular and Cerebrovascular categories.
Reference TABLES AND FIGURES: Table 100

Angina cases in UMEC, UMEC/VI and TIO

Angina cases were uncommon in the study population affecting <1.0% of participants in each cohort (see Table 25). Ten unstable events occurred among 9 (0.7%) participants in the UMEC cohort, 6 (0.2%) participants had 6 unstable angina events in the UMEC/VI cohort, and 9 (0.4%) participants had 10 unstable angina events in the TIO cohort. Angina pectoris was rare across all cohorts. Additional details on the type of angina, severity, and outcome by cohort are presented in ANNEX 2.2 – Serious adverse event: angina cases.

**Table 25 Total number of angina cases for UMEC, UMEC/VI, and TIO during observation period – FAS**

| | UMEC (N=1246) Total Events, Number of Participants, n (%) | UMEC/VI (N=2448) Total Events, Number of Participants, n (%) | TIO (N=2471) Total Events, Number of Participants, n (%) |
|---|---|---|---|
| Angina unstable | 10, 9 (0.7%) | 6, 6 (0.2%) | 10, 9 (0.4%) |
| Angina pectoris | 3, 3 (0.2%) | 7, 7 (0.3%) | 2, 2 (<0.1%) |

FAS: Full analysis set; MedDRA: Medical Dictionary for Regulatory Activities TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Included only adverse events noted as serious.
MedDRA v25.1 used.
Reference TABLES AND FIGURES: Table 96.0

Incidence rates for serious cardiovascular and cerebrovascular adverse events of special interests

At least 1 cardiovascular or cerebrovascular AESI occurred among 132 (10.6%), 288 (11.8%), and 250 (10.1%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively (see Table 26). The incidence rate (95% CI) was highest in the UMEC/VI cohort at 4.75 (4.219, 5.334), followed by the UMEC cohort at 4.70 (3.936, 5.578), and then the TIO cohort at 3.82 (3.357, 4.319) CV or cerebrovascular AESIs per 100 person-years.

**Table 26 Incidence rates and event rates for cardiovascular and cerebrovascular adverse events of special interest for UMEC, UMEC/VI and TIO during exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Number (%) of Participants with: | | | |
| No events | 1114 (89.4) | 2160 (88.2) | 2221 (89.9) |
| 1 event | 94 (7.5) | 223 (9.1) | 185 (7.5) |
| ≥2 events | 38 (3.0) | 65 (2.7) | 65 (2.6) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2806.1 | 6060.9 | 6552.9 |
| Number of First Events | 132 | 288 | 250 |
| Incidence Rate per 100 Person-Years[2] | 4.70 | 4.75 | 3.82 |
| (95% CI) | (3.936, 5.578) | (4.219, 5.334) | (3.357, 4.319) |
| Incidence Rate Ratio (unadjusted) | 1.23 | 1.25 | reference |
| (95% CI) | (0.999, 1.522) | (1.051, 1.475) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 177 | 394 | 352 |
| Event Rate per 100 Person-Years[3] | 5.46 | 5.60 | 4.80 |
| (95% CI) | (4.684, 6.325) | (5.063, 6.184) | (4.308, 5.324) |
| Event Rate Ratio (unadjusted) | 1.14 | 1.17 | reference |
| (95% CI) | (0.950, 1.363) | (1.012, 1.349) | |

CI: Confidence interval; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis.
Reference TABLES AND FIGURES: Table 42.0 and Table 81.0

### 10.4.3.5. Summary of individual case safety reports of confirmed events of interest

The highest number of MI and sudden cardiac death appeared in the UMEC/VI cohort. Analysis of the 25 sudden cardiac death cases revealed that none of the reported deaths were considered related to UMEC/VI by the investigators. In 17 cases, patients had a medical history of cardiovascular diseases (11 cases), neoplasm (3 cases), diabetes (3 cases). In 11 cases, the patients reported having a smoking history. One case concerned an elderly patient in poor social and living care. The patient age was provided in 24 cases and was 50-85 years (median: 72 years). Five cases were poorly documented and did not provide sufficient information to make any conclusions on causal relationship between UMEC/VI and sudden cardiac death.

There were 26 cases of MI in UMEC/VI cohort. None of them was considered related by the investigator. In 24 cases, the patients had a medical history. The most common items within the medical history were smoking history (14 cases), hypertension (10 cases), and other cardiovascular disorders (8 cases). The patient age was provided in all cases and was 53-82 years (median: 64 years). Twenty-one patients recovered from the MI while the

therapy was ongoing. In 1 case, therapy was interrupted due to the MI and the dechallenge was positive, however there were other episodes of MI and coronary arterial stent insertion in the medical history. There was 1 fatal case, however the cause of death was reported as atrial fibrillation.

#### 10.4.3.6. Pregnancy assessment

There was 1 pregnancy documented in the EDC, however due to the patient's age it is unlikely the patient was pregnant as the participant was PPD of age at enrollment. No pregnancies in study participants had been identified, hence no new information on pregnancies based on the results of this study are available.

### 10.4.4. Effectiveness outcomes

#### 10.4.4.1. Persistence with study medication

Time to medication discontinuation or switch

Discontinuation of or switching from the study drug was most frequent in the UMEC cohort (607 of 1236 participants analyzed) and of similar frequency in the UMEC/VI and TIO cohorts (896 of 2429 and 855 of 2458 participants analyzed, respectively). The adjusted HRs (95% CI) for medication discontinuation or switch for the UMEC and UMEC/VI cohorts compared to the TIO cohort were 1.537 (1.374, 1.718) and 1.108 (1.000, 1.226), respectively (see Table 27).

**Table 27 Time to medication discontinuation or switch for UMEC or UMEC/VI compared to TIO during exposure period – FAS**

| Exposure or Contrast | N | n | Events | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|
| UMEC | 1246 | 1236 | 607 | |
| TIO | 2471 | 2458 | 855 | |
| UMEC vs TIO | | | | 1.537 (1.374, 1.718) |
| UMEC/VI | 2448 | 2429 | 896 | |
| TIO | 2471 | 2458 | 855 | |
| UMEC/VI vs TIO | | | | 1.108 (1.000, 1.226) |

N: total number of participants in each treatment group; n: number per treatment group that are included in the analysis represented by this table; CAT: COPD Assess
ment Test; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; FAS: Full analysis set; $FEV_1$: Forced Expiratory Volume in one Second; ICS: inhaled corticosteroids; IPTW: Inverse Probability of Treatment Weighting; MI: myocardial infarction; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: All coefficients were estimated using stabilized IPTW weights. Additional statistical adjustment for confounders included country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; history of MI, Stroke, heart failure; ethnicity; physician specialty; education; ICS use at baseline; and time-varying use of add-on COPD medication. UMEC vs TIO also included history of COPD exacerbation.
Reference TABLES AND FIGURES: Table 44.0 and Table 83.0

Persistence and adherence to study medication

Estimating persistence and adherence using the PDC and MPR approach is detailed in Section 9.9.2.

PDC per year was not substantially different between the UMEC PSM cohort compared to the TIO PSM cohort. The mean (SD) PDC in Year 1 was 0.880 (0.2770) and 0.922 (0.2273) for participants in the UMEC and TIO PSM cohorts, respectively, and 0.762 (0.4075) and 0.838 (0.3512) in Year 2 (see ANNEX 1 – TLFs Table 84.0). Persistence with the study medication was similar between the UMEC/VI and TIO PSM cohorts with a mean PDC of approximately 0.93 in Year 1 and 0.85 in Year 2 (see ANNEX 1 – TLFs Table 45.0).

Medication adherence was defined as an MPR of ≥80%. Adherence was only slightly lower in the UMEC cohort compared to the TIO cohort with 521 (47.8%) vs 540 (52.1%) participants an MPR of ≥80% (see Table 28). The MPR in the UMEC/VI and TIO PSM cohorts were similar with 681 (49.6%) participants in the UMEC/VI and 671 (51.4%) participants in the TIO cohorts considered adherent.

**Table 28 Medication possession ratio for UMEC or UMEC/VI versus TIO – PSM cohorts**

| | UMEC or UMEC/VI | TIO | Odds Ratio (95% CI) |
|---|---|---|---|
| **UMEC vs TIO** | **(N=1114)** | **(N=1114)** | |
| Medication Possession Ratio ≥80% | | | |
| n | 1091 | 1037 | |
| Yes, n (%) | 521 (47.8) | 540 (52.1) | 0.84 (0.71,1.00) |
| No, n (%) | 570 (52.2) | 497 (47.9) | |
| | | | |
| **UMEC/VI vs TIO** | **(N=1404)** | **(N=1404)** | |
| Medication Possession Ratio ≥80% | | | |
| n | 1373 | 1305 | |
| Yes, n (%) | 681 (49.6) | 671 (51.4) | 0.93 (0.80, 1.08) |
| No, n (%) | 692 (50.4) | 634 (48.6) | |

CI: Confidence interval; MPR: Medication possession ratio; PSM: Propensity score matched; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Odds Ratio and 95% CI were drawn from a logistic regression model (UMEC versus Tiotropium).
A participant had to have at least 2 prescriptions for the index medication without a switch between them in order to be included in the MPR calculation.
Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 46.0 and Table 85.0

### 10.4.4.2. Incidence rate and frequency of moderate/severe COPD exacerbation

Overall incidence rate and frequency of moderate/severe COPD exacerbation

At least 1 moderate/severe COPD exacerbation occurred among 264 (21.2%), 453 (18.5%), and 540 (21.9%) participants in the UMEC, UMEC/VI, and TIO cohorts, respectively (see Table 29). The incidence rate (95% CI) of moderate/severe COPD exacerbation was lowest among participants in the UMEC/VI cohort (7.42 [6.753, 8.137] moderate/severe exacerbations per 100 person-years), slightly higher in the TIO cohort (8.83 [8.101, 9.607]

moderate/severe exacerbations per 100 person-years), and highest in the UMEC cohort (9.56 [8.445, 10.790] moderate/severe exacerbations per 100 person-years).

**Table 29 Effectiveness Outcomes: Incidence and event rates of moderate/severe COPD exacerbations for UMEC/VI, UMEC, and TIO in exposure period – FAS**

| | UMEC (N=1246) | UMEC/VI (N=2448) | TIO (N=2471) |
|---|---|---|---|
| Number (%) Participants with: | | | |
| No events | 982 (78.8) | 1995 (81.5) | 1931 (78.1) |
| 1 event | 140 (11.2) | 274 (11.2) | 261 (10.6) |
| ≥2 events | 124 (10.0) | 179 (7.3) | 279 (11.3) |
| **Incidence Rate** | | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2760.4 | 6104.4 | 6115.4 |
| Number of First Events | 264 | 453 | 540 |
| Incidence Rate per 100 Person-Years[2] | 9.56 | 7.42 | 8.83 |
| (95% CI) | (8.445, 10.790) | (6.753, 8.137) | (8.101, 9.607) |
| Incidence Rate Ratio (unadjusted) | 1.08 | 0.84 | reference |
| (95% CI) | (0.935, 1.255) | (0.742, 0.952) | |
| **Event Rate** | | | |
| Sum of Person-Time (Years) Exposure Period | 3242.5 | 7032.6 | 7339.3 |
| Total Number of Events | 609 | 847 | 1267 |
| Event Rate per 100 Person-Years[3] | 18.78 | 12.04 | 17.26 |
| (95% CI) | (17.320, 20.335) | (11.246, 12.883) | (16.326, 18.241) |
| Event Rate Ratio (unadjusted) | 1.09 | 0.70 | reference |
| (95% CI) | (0.988, 1.198) | (0.640, 0.761) | |

CI: Confidence interval; COPD: Chronic obstructive pulmonary disesae; FAS: Full analysis set; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for Event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis.
Reference TABLES AND FIGURES: Table 47.0 and Table 86.0

Risk of moderate/severe COPD exacerbation

The adjusted HR (95% CI) for moderate/severe COPD exacerbations was 0.919 (0.786, 1.074) and 0.966 (0.849, 1.101) for UMEC vs TIO cohorts and UMEC/VI vs TIO cohorts, respectively (see Table 30).

The rate of moderate/severe COPD exacerbations in the UMEC cohort was almost 2 times the rate of the TIO cohort (rate ratio [95% CI]: 1.976 [1.616, 2.416]). Participants in the UMEC/VI cohorts had a similar rate of moderate/severe COPD exacerbations compared to the TIO cohort (rate ratio [95% CI]: 1.072 [0.900, 1.277]) (see Table 31).

**Table 30 Risk of moderate/severe COPD exacerbation for UMEC or UMEC/VI compared to TIO during exposure period – FAS**

| Exposure or Contrast | N | n | Events | Adjusted Hazard Ratio (95% CI) |
|---|---|---|---|---|
| UMEC | 1246 | 1236 | 263 | |
| TIO | 2471 | 2458 | 538 | |
| UMEC vs TIO | | | | 0.919 (0.786,1.074) |
| UMEC/VI | 2448 | 2429 | 452 | |
| TIO | 2471 | 2458 | 538 | |
| UMEC/VI vs TIO | | | | 0.966 (0.849,1.101) |

N: total number of participants in each treatment group; n: number per treatment group that are included in the analysis represented by this table; CAT: COPD Assessment Test; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced Expiratory Volume in one Second; ICS: inhaled corticosteroids; IPTW: Inverse Probability of Treatment Weighting; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: All coefficients were estimated using stabilized IPTW weights. Additional statistical adjustment for confounders included country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; ethnicity; physician specialty; ICS use at enrollment; history of COPD exacerbation; and time-varying use of add-on COPD medication. UMEC vs TIO also included education and history of COPD exacerbation.
Reference TABLES AND FIGURES: Table 49.0 and Table 88.0

**Table 31 Rate ratios and 95% CI using negative binomial model for moderate/severe COPD exacerbation in UMEC or UMEC/VI versus TIO during exposure period – FAS**

| Exposure or Contrast | Events | Rate Ratio (95% CI) |
|---|---|---|
| UMEC | 608 | |
| TIO | 1261 | |
| UMEC vs TIO | | 1.976 (1.616, 2.416) |
| UMEC/VI | 846 | |
| TIO | 1261 | |
| UMEC/VI vs TIO | | 1.072 (0.900, 1.277) |

n: number of participants included in the analysis per treatment group; CAT: COPD Assessment Test; CI: confidence interval; COPD: Chronic obstructive pulmonary disease; $FEV_1$: Forced Expiratory Volume in one Second; ICS: inhaled corticosteroids; TIO: Tiotropium; UMEC: Umeclidinium bromide; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
Note: For UMEC vs TIO and UMEC/VI vs TIO: Results were estimated from a negative binomial regression model adjusting for country of enrollment; age at enrollment; gender; $FEV_1$ % predicted at enrollment; smoking status at enrollment; CAT score; quadratic and cubic terms for age, $FEV_1$ % predicted at enrollment and CAT score; ethnicity; physician specialty; History of COPD exacerbation at baseline; and ICS use at baseline.
More than one exacerbation event can be counted per participant.
The 95% Confidence Intervals were calculated assuming a negative binomial distribution.
Reference TABLES AND FIGURES: Table 89.0 and Table 50.0

Incidence rate and frequency of moderate/severe COPD exacerbation requiring hospitalization

At least 1 COPD exacerbation requiring hospitalization occurred among 45 (4.0%) and 46 (4.1%) participants in the UMEC and TIO PSM cohorts, respectively (see Table 32).

The incidence rates (95% CI) were 1.59 (1.572, 2.122) and 1.44 (1.052, 1.917) moderate/severe COPD exacerbations requiring hospitalization per 100 person-years among the UMEC and TIO PSM cohorts, respectively.

At least 1 COPD exacerbation requiring hospitalization occurred among 56 (4.0%) and 57 (4.1%) participants in the UMEC/VI and TIO PSM cohorts, respectively. The incidence rates (95% CI) were similar at 1.40 (1.056, 1.815) and 1.44 (1.089, 1.862) moderate/severe COPD exacerbations requiring hospitalization per 100 person-years for the UMEC/VI and TIO PSM cohorts, respectively.

**Table 32 Effectiveness Outcomes: Incidence and event rates of moderate/severe COPD exacerbations requiring hospitalization, UMEC or UMEC/VI versus TIO in exposure period – PSM cohorts**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| Number (%) Participants with: | | |
| No events | 1069 (96.0) | 1068 (95.9) |
| 1 event | 38 (3.4) | 39 (3.5) |
| ≥2 events | 7 (0.6) | 7 (0.6) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 2838.1 | 3200.2 |
| Number of First Events | 45 | 46 |
| Incidence Rate per 100 Person-Years[2] | 1.59 | 1.44 |
| (95% CI) | (1.157, 2.122) | (1.052, 1.917) |
| Incidence Rate Ratio | 1.10 | reference |
| (95% CI) | (0.731, 1.664) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 2922.0 | 3292.5 |
| Total Number of Events | 55 | 61 |
| Event Rate per 100 Person-Years[3] | 1.88 | 1.85 |
| (95% CI) | (1.418, 2.450) | (1.417, 2.380) |
| Event Rate Ratio | 1.02 | reference |
| (95% CI) | (0.706, 1.463) | |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| Number (%) Participants with: | | |
| No events | 1348 (96.0) | 1347 (95.9) |
| 1 event | 41 (2.9) | 50 (3.6) |
| ≥2 events | 15 (1.1) | 7 (0.5) |
| **Incidence Rate** | | |
| Sum of Person-Time (Years) Exposure Period to the first event[1] | 4006.8 | 3965.4 |
| Number of First Events | 56 | 57 |
| Incidence Rate per 100 Person-Years[2] | 1.40 | 1.44 |
| (95% CI) | (1.056, 1.815) | (1.089, 1.862) |
| Incidence Rate Ratio | 0.97 | reference |
| (95% CI) | (0.672, 1.406) | |
| **Event Rate** | | |
| Sum of Person-Time (Years) Exposure Period | 4117.3 | 4073.9 |
| Total Number of Events | 75 | 65 |

| | | |
|---|---|---|
| Event Rate per 100 Person-Years[3] | 1.82 | 1.60 |
| (95% CI) | (1.433, 2.283) | (1.231, 2.034) |
| Event Rate Ratio | 1.14 | reference |
| (95% CI) | (0.819, 1.591) | |

CI: Confidence interval; PSM: Propensity score matched; TIO: Tiotropium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 Time after the first event was not included in Person-time for Incidence but was counted for event rate.
2 Incidence rate = number of first events per 100 person-years.
3 Event rate = total number of events per 100 person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 51.0 and Table 90.0

#### 10.4.4.3. All-cause and COPD-related health care utilization

All-cause health care utilization

*UMEC vs TIO – PSM cohorts*

Participants in the UMEC and TIO PSM cohorts largely reported either no HCP visits during the exposure period (UMEC: n=429, 38.5%; TIO: n=366, 32.9%) or 5 or more visits (UMEC: n=423, 38.0%; TIO: n=523, 46.9%) (see Table 33). HCP visit rates were similar at 357.22 and 353.05 visits per 100 person-years among participants in the UMEC and TIO PSM cohorts, respectively, with a relative rate (95% CI) of 1.012 (0.985, 1.039) in the UMEC PSM cohort compared to the TIO PSM cohort.

During the exposure period, 195 (17.5%) participants in the UMEC PSM cohort and 187 (16.8%) participants in the TIO PSM cohort were hospitalized 1-2 times. Hospitalization was more frequent in the UMEC PSM cohort than in the TIO PSM cohort (UMEC: 14.92 hospitalizations per 100 person-years; TIO: 12.30 hospitalizations per 100 person-years) with a relative rate (95% CI) of 1.213 (1.060, 1.389).

During the exposure period, 171 (15.4%) participants in the UMEC PSM cohort and 187 (16.8%) participants in the TIO PSM cohort had 1-2 ED visits. ED visit rates were lower in the UMEC PSM cohort compared to the TIO PSM cohort (UMEC: 13.14 ED visits per 100 person-years; TIO: 15.34 ED visits per 100 person-years), with a relative rate (95% CI) of 0.857 (0.750, 0.978).

*UMEC/VI vs TIO – PSM cohorts*

In the TIO PSM cohort, an equal number of participants reported no visits and 5 or more HCP visits during the exposure period (n=552, 39.3%). In the UMEC/VI PSM cohort, 560 (39.9%) participants had no HCP visits, and 504 (35.9%) participants had 5 or more visits. HCP visit rates were lower in the UMEC/VI PSM cohort compared to the TIO PSM cohort (UMEC/VI: 269.08 visits per 100 person-years; TIO: 282.14 visits per 100 person-years), with a relative rate (95% CI) of 0.954 (0.929, 0.979).

During the exposure period, 213 (15.2%) participants in the UMEC/VI PSM cohort and 205 (14.6%) participants in the TIO PSM cohort had 1-2 hospitalizations. Hospitalization rates were higher in the UMEC/VI PSM cohort compared to the TIO PSM cohort

(UMEC/VI: 12.27 hospitalizations per 100 person-years; TIO:10.14 hospitalizations per 100 person-years), with a relative rate (95% CI) of 1.210 (1.062, 1.378).

Both UMEC/VI and TIO PSM cohorts had 175 (12.5%) participants with 1-2 ED visits during the exposure period. ED visit rates were similar between the cohorts (UMEC/VI: 10.01 visits per 100 person-years; TIO: 11.14 visits per 100 person-years), with a relative rate (95% CI) of 0.898 (0.786, 1.026).

**Table 33 All-cause healthcare utilization for UMEC versus TIO during exposure period – PSM cohort**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| **HCP Visits** | | |
| 0 Visits, n (%) | 429 (38.5) | 366 (32.9) |
| 1-2 Visits, n (%) | 178 (16.0) | 129 (11.6) |
| 3-4 Visits, n (%) | 84 (7.5) | 96 (8.6) |
| 5+ Visits, n (%) | 423 (38.0) | 523 (46.9) |
| Total HCP Visits | 10438 | 11624 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 357.22 | 353.05 |
| Relative Rate (95% CI)[1] | 1.012 (0.985, 1.039) | reference |
| **Hospitalizations** | | |
| 0 Hospitalizations, n (%) | 874 (78.5) | 885 (79.4) |
| 1-2 Hospitalization(s), n (%) | 195 (17.5) | 187 (16.8) |
| 3-4 Hospitalizations, n (%) | 33 (3.0) | 29 (2.6) |
| 5+ Hospitalizations, n (%) | 12 (1.1) | 13 (1.2) |
| Total Hospitalizations | 436 | 405 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 14.92 | 12.30 |
| Relative Rate (95% CI)[1] | 1.213 (1.060, 1.389) | reference |
| **Emergency Department Visits** | | |
| 0 Visit, n (%) | 907 (81.4) | 869 (78.0) |
| 1-2 Visits, n (%) | 171 (15.4) | 187 (16.8) |
| 3-4 Visits, n (%) | 21 (1.9) | 34 (3.1) |
| 5+ Visits, n (%) | 15 (1.3) | 24 (2.2) |
| Total Emergency Department Visits | 384 | 505 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 13.14 | 15.34 |
| Relative Rate (95% CI)[1] | 0.857 (0.750, 0.978) | reference |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| **HCP Visits** | | |
| 0 Visits, n (%) | 560 (39.9) | 552 (39.3) |
| 1-2 Visits, n (%) | 234 (16.7) | 179 (12.7) |
| 3-4 Visits, n (%) | 106 (7.5) | 121 (8.6) |
| 5+ Visits, n (%) | 504 (35.9) | 552 (39.3) |
| Total HCP Visits | 11079 | 11494 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 269.08 | 282.14 |
| Relative Rate (95% CI)[1] | 0.954 (0.929, 0.979) | reference |
| **Hospitalizations** | | |

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| 0 Hospitalizations, n (%) | 1138 (81.1) | 1161 (82.7) |
| 1-2 Hospitalization(s), n (%) | 213 (15.2) | 205 (14.6) |
| 3-4 Hospitalizations, n (%) | 36 (2.6) | 26 (1.9) |
| 5+ Hospitalizations, n (%) | 17 (1.2) | 12 (0.9) |
| Total Hospitalizations | 505 | 413 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 12.27 | 10.14 |
| Relative Rate (95% CI)[1] | 1.210 (1.062, 1.378) | reference |
| **Emergency Department Visits** | | |
| 0 Visit, n (%) | 1184 (84.3) | 1178 (83.9) |
| 1-2 Visits, n (%) | 175 (12.5) | 175 (12.5) |
| 3-4 Visits, n (%) | 30 (2.1) | 30 (2.1) |
| 5+ Visits, n (%) | 15 (1.1) | 21 (1.5) |
| Total Emergency Department Visits | 412 | 454 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 10.01 | 11.14 |
| Relative Rate (95% CI)[1] | 0.898 (0.786, 1.026) | reference |

CI: Confidence interval; HCP: healthcare provider; PSM: Propensity score matched; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
[1] 95% CI based on Poisson distribution.
Rate per 100 person-years was calculated as 100 times the number of events divided by the sum or person-years. The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 55.0 and Table 94.0

COPD-related health care utilization

*UMEC vs TIO – PSM cohorts*

More than half of participants in the UMEC and TIO PSM cohorts did not have any COPD-related HCP visits during the exposure period (see Table 34). There were 177 (15.9%) and 200 (18.0%) participants in the UMEC and TIO PSM cohorts, respectively, with during the exposure period. There were also 164 (14.7%) and 224 (20.1%) participants in the UMEC and TIO PSM cohorts, respectively, with 5 or more COPD-related HCP visits during the exposure period. The COPD-related HCP visit rates were lower among participants in the UMEC PSM cohort (UMEC: 72.69 visits per 100 person-years TIO: 91.18 visits per 100 person-years), with a relative rate (95% CI) of 0.797 (0.754, 0.843).

COPD-related hospitalizations were uncommon with 52 (4.7%) participants in the UMEC PSM cohort and 62 (5.6%) participants in the TIO PSM cohort that had 1-2 COPD-related hospitalizations during the exposure period. COPD-related hospitalization rates similar between the 2 cohorts (UMEC: 2.98 hospitalizations per 100 person-years; TIO: 2.52 hospitalizations per 100 person-years), with a relative rate (95% CI) of 1.181 (0.874, 1.595).

Similarly, COPD-related ED visits were also uncommon with 47 (4.2%) participants in the UMEC PSM cohort and 64 (5.7%) participants in the TIO PSM cohort that had 1-2 COPD-related ED visits during the exposure period. COPD-related ED visit rates were similar between the 2 cohorts (UMEC: 2.87 visits per 100 person-years; TIO: 3.64 visits per 100 person-years), with a relative rate (95% CI) of 0.789 (0.597, 1.042).

*UMEC/VI vs TIO – PSM cohorts*

Over 60% of the UMEC/VI and TIO PSM cohort did not have any COPD-related HCP visits during the exposure period. There were 239 (17.0%) and 214 (15.2%) participants in the UMEC/VI and TIO PSM cohorts, respectively, with 1-2 COPD-related HCP visits during the exposure period. There were also 143 (10.2%) and 227 (16.2%) participants in the UMEC/VI and TIO PSM cohorts, respectively, with 5 or more COPD-related HCP visits during the exposure period. The COPD-related HCP visit rates were lower among participants in the UMEC/VI PSM cohort (UMEC/VI: 54.40 visits per 100 person-years TIO: 78.06 visits per 100 person-years), with a relative rate (95% CI) of 0.697 (0.660, 0.736).

COPD-related hospitalizations were uncommon with 62 (4.4%) participants in the UMEC/VI PSM cohort and 69 (4.9%) participants in the TIO PSM cohort that had 1-2 COPD-related hospitalizations during the exposure period. COPD-related hospitalization rates are similar between the 2 cohorts (UMEC/VI: 2.84 hospitalizations per 100 person-years; TIO: 2.33 hospitalizations per 100 person-years), with a relative rate (95% CI) of 1.219 (0.930, 1.597).

Similarly, COPD-related ED visits were also uncommon with 44 (3.1%) participants in the UMEC/VI PSM cohort and 69 (4.9%) participants in the TIO PSM cohort that had 1-2 COPD-related ED visits during the exposure period. COPD-related ED visit rates were lower in the UMEC/VI PSM cohort compared to the TIO cohort (UMEC/VI: 1.92 visits per 100 person-years; TIO: 2.70 visits per 100 person-years), with a relative rate (95% CI) of 0.711 (0.532, 0.949).

**Table 34 COPD-related healthcare utilization for UMEC or UMEC/VI versus TIO during exposure period – PSM cohorts**

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| **UMEC versus TIO** | **(N=1114)** | **(N=1114)** |
| **HCP Visits** | | |
| 0 Visits, n (%) | 704 (63.2) | 601 (53.9) |
| 1-2 Visits, n (%) | 177 (15.9) | 200 (18.0) |
| 3-4 Visits, n (%) | 69 (6.2) | 89 (8.0) |
| 5+ Visits, n (%) | 164 (14.7) | 224 (20.1) |
| Total HCP Visits | 2124 | 3002 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 72.69 | 91.18 |
| Relative Rate (95% CI)[1] | 0.797 (0.754, 0.843) | reference |
| **Hospitalizations** | | |
| 0 Hospitalizations, n (%) | 1056 (94.8) | 1050 (94.3) |
| 1-2 Hospitalization(s), n (%) | 52 (4.7) | 62 (5.6) |
| 3-4 Hospitalizations, n (%) | 4 (0.4) | 1 (0.1) |
| 5+ Hospitalizations, n (%) | 2 (0.2) | 1 (0.1) |
| Total Hospitalizations | 87 | 83 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 2.98 | 2.52 |
| Relative Rate (95% CI)[1] | 1.181 (0.874, 1.595) | reference |
| **Emergency Department Visits** | | |
| 0 Visit, n (%) | 1059 (95.1) | 1039 (93.3) |

| | UMEC or UMEC/VI | TIO |
|---|---|---|
| 1-2 Visits, n (%) | 47 (4.2) | 64 (5.7) |
| 3-4 Visits, n (%) | 8 (0.7) | 9 (0.8) |
| 5+ Visits, n (%) | 0 (0.0) | 2 (0.2) |
| Total Emergency Department Visits | 84 | 120 |
| Person-Time (Years) | 2922.0 | 3292.5 |
| Rate per 100 Person-Years | 2.87 | 3.64 |
| Relative Rate (95% CI)[1] | 0.789 (0.597, 1.042) | reference |
| | | |
| **UMEC/VI versus TIO** | **(N=1404)** | **(N=1404)** |
| **HCP Visits** | | |
| 0 Visits, n (%) | 946 (67.4) | 866 (61.7) |
| 1-2 Visits, n (%) | 239 (17.0) | 214 (15.2) |
| 3-4 Visits, n (%) | 76 (5.4) | 97 (6.9) |
| 5+ Visits, n (%) | 143 (10.2) | 227 (16.2) |
| Total HCP Visits | 2240 | 3180 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 54.40 | 78.06 |
| Relative Rate (95% CI)[1] | 0.697 (0.660, 0.736) | reference |
| **Hospitalizations** | | |
| 0 Hospitalizations, n (%) | 1332 (94.9) | 1331 (94.8) |
| 1-2 Hospitalization(s), n (%) | 62 (4.4) | 69 (4.9) |
| 3-4 Hospitalizations, n (%) | 8 (0.6) | 3 (0.2) |
| 5+ Hospitalizations, n (%) | 2 (0.1) | 1 (0.1) |
| Total Hospitalizations | 117 | 95 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 2.84 | 2.33 |
| Relative Rate (95% CI)[1] | 1.219 (0.930, 1.597) | reference |
| **Emergency Department Visits** | | |
| 0 Visit, n (%) | 1351 (96.2) | 1327 (94.5) |
| 1-2 Visits, n (%) | 44 (3.1) | 69 (4.9) |
| 3-4 Visits, n (%) | 8 (0.6) | 7 (0.5) |
| 5+ Visits, n (%) | 1 (0.1) | 1 (0.1) |
| Total Emergency Department Visits | 79 | 110 |
| Person-Time (Years) | 4117.3 | 4073.9 |
| Rate per 100 Person-Years | 1.92 | 2.70 |
| Relative Rate (95% CI)[1] | 0.711 (0.532, 0.949) | reference |

CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; HCP: healthcare provider; PSM: Proposensity score matched; TIO: Tiotropium; UMEC: Umeclidinium; UMEC/VI: Umeclidinium bromide/vilanterol trifenatate.
1 95% CI based on Poisson distribution.
Rate per 100 person-years was calculated as 100 times the number of events divided by the sum or person-years.
The incidence and event rates are unadjusted as these rates are only descriptive. Adjusted results are provided in the time to event analysis. Variables used for PSM are described in Section 9.9.2.
Reference TABLES AND FIGURES: Table 56.0 and Table 95.0

## 10.5. Other analyses

Not applicable.

## 10.6. Adverse events/adverse reactions

Adverse events were presented in Section 10.4.3.

### 10.6.1. Unresolved adverse events

Five AEs which should have been considered as SAEs were closed without resolution (see Table 35). For 4 out of 5 events, the event met SAE criteria per sponsor, but by the time events were queried it was not possible to upgrade to an SAE as the site was closed. Detailed description of each unresolved AEs is presented in ANNEX 2.3. The other event met SAE criteria per sponsor, however the site refused to update the AE to SAE. This query was closed without resolution. These 5 unresolved events are considered as AEs in the analysis.

**Table 35 Summary of unresolvable AE to SAE**

| Issue No. | Adverse Event (AE) | Onset date of AE | Summary |
|---|---|---|---|
| 1 | Suffocation | 17 January 2018 | Event meets SAE criteria but was not able to upgrade AE to SAE because site was closed. |
| 2 | Unstable angina pectoris | 26 March 2020 | Event meets SAE criteria but was not able to upgrade AE to SAE because site was closed. |
| 3 | Chronic Respiratory failure with hypoxia | 22 May 2017 | Event meets SAE criteria but was not able to upgrade AE to SAE because site was closed. |
| 4 | Multiple lung nodules | 14 September 2017 | Event meets SAE criteria but was not able to upgrade AE to SAE because site was closed. |
| 5 | Malignant Neoplasm of Upper Lobe of Left Lung | 10 July 2020 | Event meets SAE criteria, but AE was not upgraded to SAE. PI decided that this event did not meet SAE criteria. PI refused to update AE to SAE. |

AE: adverse event; PI: principal investigator; SAE: serious adverse event.

# 11. DISCUSSION

## 11.1. Key results

Out of 6606 participants enrolled in the study, 6165 were included in the FAS: 1246 participants were in the UMEC cohort, 2448 participants were in the UMEC/VI cohort, and 2471 were in the TIO cohort. The UMEC and TIO PSM cohorts included 1114 participants per treatment, and the UMEC/VI and TIO PSM cohorts included 1404 participants per treatment. The proportion of participants discontinuing the study were similar across the cohorts at approximately 35%. The median (Q1-Q3) duration of exposure to the study medication among participants in the UMEC cohort was 945.5 (380.0, 1512.0) days, the median (Q1-Q3) duration of exposure among participants in the UMEC/VI cohort was 1105.0 (546.5, 1592.5) days, and among participants in the TIO cohort, the median (Q1-Q3) duration of exposure was 1154.0 (560.0, 1684.0) days.

The baseline profile of the UMEC/VI cohort suggests that these participants had more severe COPD compared to the UMEC and TIO cohorts based on factors such as their prescribing physician, lung function results, and co-morbidities.

This study demonstrated that UMEC and UMEC/VI were both not inferior to TIO with regards to the risk of the composite endpoint of MI, stroke, HF, or sudden cardiac death.

The incidence rates and event rates of the composite endpoint, the individual cardiovascular endpoints, and mortality rates were low. Serious pneumonia and LRTIs were uncommon and there was no evidence to suggest that the risks differed between cohorts.

No new safety signals were identified. All-cause and cardiovascular-related mortality rates were highest among the UMEC/VI cohort. The UMEC and UMEC/VI cohorts presented higher incidence rates of SAEs and drug-related AEs compared to the TIO cohort, but rates were not adjusted by any potential confounder such as patient severity. Mortality rates were low overall, with most deaths being non-cardiovascular related.

A larger proportion of participants discontinued or switched their study drug in the UMEC cohort compared to the TIO cohort while UMEC/VI and TIO cohorts showed similar results. Adherence with study medication (medication possession ratio of ≥80%) demonstrated a similar pattern. Rates of COPD-related HCP visits and ED visits (all-cause) were lower in the UMEC cohort compared to the TIO cohort, and rates of (all-cause and COPD-related) HCP visits and COPD-related ED visits were lower in the UMEC/VI cohort compared to the TIO cohort. The UMEC and UMEC/VI cohorts both had higher rates of (all-cause) hospitalizations.

## 11.2. Limitations

The study relied on the use of data collected from participants' medical charts. Although steps were taken to limit the effect of bias and confounding, several limitations of observational study design and conduct should be noted when interpreting results of the study.

Enrolment bias: sites were expected to prospectively enroll all eligible participants that presented at their site (subject to enrolment caps on a specific treatment group) and maintained screening logs of all participants meeting eligibility criteria, along with reasons for non-enrolment of otherwise eligible participants.

Channeling bias: due to the real-world study design, factors associated with treatment choice (UMEC/VI, UMEC, or TIO) were not controlled. Although these factors were partially addressed through PS methods or other multivariate analyses, there may be residual bias that impact these treatment choices. These factors included prescribing pattern differences based on COPD severity. One biggest limitation of the study is that particiapnts with more severe COPD were likely initiated in LAMA/LABA therapy than LAMA alone. Over the course of the study, as other treatments emerged, more severe patients and those with more exacerbations were also potentially more likely to switch therapy. Based on the results presented, the composite profile of participants in the UMEC/VI cohort indicated this cohort likely had more severe COPD participants compared to the UMEC and TIO cohorts.

Healthy user bias/depletion of susceptible: long-term users of a given medication have generally shown tolerance to the drug and may be at lower risk of CV events than new users. Since participants were enrolled at the time of initiation of a new medication regimen (new user study design), this largely eliminated the bias associated with the study of prevalent medication users. It is acknowledged that participants may have used a previous LAMA medication as recently as 12 months prior to study enrolment (<1% overall); however, this liberal definition of "new user" was intended to be inclusive and representative of the population of participants who initiated use of UMEC/VI, UMEC, or TIO for COPD in order to characterize their comparative safety.

Inconsistent interpretation of eCRFs by participating centers: while instructions were provided to participating sites, it is not possible to know if certain sites performed differently from others when collecting participant baseline information. All sites used standardized documentation for completing case report forms at enrolment and for each follow-up assessment to collect data as uniformly as possible.

Follow-up bias: Participants who were lost to follow-up may differ from those who remained in the study. Efforts were made to follow-up directly with participants even if they did not return to the enrolling center and participants were asked at the 6- and 18-month follow-ups if they had changed their health care provider and if so to provide the name and contact information for their new physician.

Representativeness of COPD population: The study's new user design enrolled participants newly prescribed UMEC/VI, UMEC or TIO for COPD. While the selection of study sites and countries were planned to be reflective of the subpopulation of COPD participants initiating new treatment, these participants may differ from the broader population of COPD participants. They were expected to comprise either of younger and less severe participants recently diagnosed or previously managed with only short-acting medicines or participants adding LAMA to ICS/LABA who may be more severe participants with exacerbations or asthma-COPD overlap syndrome. While this is not a limitation or challenge to the internal validity of the study in addressing its primary and secondary objectives among participants meeting the study inclusion and exclusion criteria, it should be noted as a potential limitation to the extrapolation of the results to the broader population of COPD participants.

Recruitment of participants treated with newly approved medications: uptake of new products such as UMEC/VI and UMEC was unpredictable. While there were an estimated sample size of 2233 participants per treatment cohort, the UMEC cohort was not able to enroll as many participants.

Missing data: There were several variables in the study with missing information. Large amount of missing information limited the number of variables included in the PSM model. Some variables were dropped because of the high proportion of missing data.

## 11.3. Interpretation

This study was a multinational, prospective, observational, nonrandomized PASS to evaluate whether the incidence rates of CV and cerebrovascular events differed for new users of UMEC or UMEC/VI combination compared with new users of TIO in participants

diagnosed with COPD. The purpose of the study was to collect data reflecting the 'real-world' experience with UMEC and UMEC/VI combination in the post-approval setting to expand the understanding of potential CV and cerebrovascular risks (MI, stroke, heart failure and sudden cardiac death) in COPD participants. The study data represents the clinical practice in selected countries in Europe and the US with 358 centers throughout 9 European countries and the US (US enrollment capped at approximately 50%).

This study demonstrated that both UMEC and UMEC/VI were not inferior to TIO for the composite endpoint. This key finding shows that the risk of the composite endpoint of MI, stroke, heart failure, or sudden cardiac death was not higher among participants treated with UMEC or UMEC/VI than participants treated with TIO. It is important to note that the incidence rate of the composite endpoint was low across all cohorts.

The study also assessed the risk of MI, stroke, and heart failure between UMEC or UMEC/VI compared to TIO and found no difference for stroke and heart failure. For MI, an increased risk was found for the UMEC/VI cohort compared to the TIO cohort, but a thorough analysis of individual case safety reports did not suggest that any of the confirmed events were related to UMEC/VI. The incidence of MI was low across all cohorts (incidence rates [95% CI] - UMEC: 0.28 [0.127, 0.529] per 100 person-years; UMEC/VI: 0.37 [0.243, 0.546] per 100 person-years; and TIO: 0.21 [0.115, 0.338] per 100 person-years) and compared with the literature. A previous study investigated CV risk among COPD participants treated with TIO and reported an incidence rate of the CV composite endpoint (CV death, MI, and stroke) of 2.15 per 100 person-years. Another study found no difference in risk of overall cardiovascular outcomes between new LABA and TIO users, however the study did report an increased risk of ischemic stroke among TIO users compared to LABA users (adjusted odds ratio [95% CI]=1.73 [1.06, 2.83]) [Gershon, 2013]. Another comparative study found no difference in risk of stroke among TIO users compared to LABA users (HR [95% CI]=1.49 [0.91, 2.45]) [Jara, 2012]. Finally, a recent population-based cohort study also found no difference on risks of acute myocardial infarction (AMI), stroke, and major adverse cardiovascular events (MACE) among LAMA, LAMA/LABA, LABA/ICS and TIO users compared to LABA users [Rebordosa, 2022].

The number of cases and incidence rates for MI, stroke, and heart failure were low across all cohorts in the study. The incidence rates of MI, heart failure, and stroke across all cohorts was <0.6 per 100 person-years, which is lower than incidence rates reported from other studies. A recent retrospective study on UMEC and UMEC/VI using UK electronic health record databases found MI incidence rates (95% CI) of 0.69 (0.44, 1.02) and 0.68 (0.35, 1.19) per 100 person-years among UMEC and UMEC/VI users, respectively [Requena, 2021]. The incidence rates (95% CI) for stroke were 3.09 (2.53, 3.74) and 3.05 (2.28, 3.98) per person-years in UMEC and UMEC/VI users, respectively. Another study reported incidence rates of 1.27, 3.40, and 1.64 per 100 person-years for MI, heart failure, and stroke among TIO users, and among LABA users the incidence rates for MI, heart failure and stroke were 1.0, 4.64, and 1.22 per 100 person-years, respectively [Jara, 2012].

The minor differences observed in MI, stroke and heart failure incidence rates between cohorts, specifically UMEC/VI users compared to TIO users, may also be attributable to varying country-specific cardiovascular disease burden. In general, Eastern European

countries have higher cardiovascular disease burden compared to other European countries and the US [Vaduganathan, 2022]. Confounding by indication may have also likely contributed to differences observed between the UMEC/VI and TIO cohorts.

The UMEC/VI cohort had a slightly higher sudden cardiac death rate compared to the other cohorts, however the overall number of sudden cardiac deaths in the study was low. The overall all-cause mortality rate in the study was 1.652 per 100 person-years with the highest mortality rate observed in the UMEC/VI cohort (mortality rate=2.033 per 100 person-years). CV-related mortality rate was also highest in the UMEC/VI cohort with a mortality rate of 0.355 per 100 person-years. The baseline clinical characteristics of participants in the UMEC/VI cohort somewhat indicated that participants in this cohort were more ill compared to the other cohorts, which may contribute to slightly higher mortality rate in the UMEC/VI cohort than the other cohorts. Nevertheless, the all-cause and CV-related mortality rates in the study were generally lower compared to previous studies. A recent retrospective study reported all-cause mortality rates of 2.99 and 3.51 per 100 person-years in UMEC and UMEC/VI users, and a CV-related mortality rate of 1.64 among UMEC/VI users [Requena, 2021]. Another study using clinical trial safety databases reported all-cause mortality rate of 3.474 per 100 person-years and a cardiovascular-related mortality rate of 0.98 per 100 person-years among TIO users [Celli, 2010].

The baseline profile of the UMEC/VI cohort suggests that participants in this cohort had more severe COPD compared to the UMEC and TIO cohorts. Participants in the UMEC/VI cohort had a slightly lower mean $FEV_1$ % predicted. These participants also had lower mean time from spirometry to enrollment compared to the UMEC and TIO cohorts which suggest a more recent contact with healthcare providers and potentially a greater need for regular COPD surveillance. The primary prescribing physicians for UMEC/VI were pulmonologists, which also suggests that UMEC/VI participants had more severe disease. The UMEC/VI cohort had higher proportions of participants with history of AF and LBBB, which are major risk markers of cardiovascular disease and poorer outcome [Odutayo, 2016; Zannad, 2007]. Also, a higher proportion of participants in the UMEC/VI cohort previously received LABA or theophylline compared to the other cohorts. Participants with more severe COPD are more likely to initiate dual LAMA/LABA therapy than LAMA only therapy. The study used PS methods and other multivariate analyses to mitigate the impact of these biases in the comparisons between cohorts, however some residual confounding may still be present.

Participants in this study were evaluated using the GOLD 2019 standard to guide COPD treatment decisions. About 70% of the participants with available data on GOLD 2019 classification were grouped in Group B (0 or 1 moderate exacerbations with mMRC ≥2 and CAT ≥10) (UMEC=63.9; UMEC/VI=71.8%; and TIO=67.6%), and about 28% were classified in Group A (0 or 1 moderate exacerbations with mMRC 0-1 and CAT <10). A small proportion of participants were grouped in Group C (0.4%) and 3.3% were in Group D, which includes COPD patients with ≥2 moderate exacerbation or ≥1 leading to hospitalization. The proportion of Group B remained unchanged after participants were reclassified using the GOLD 2023 classification, and participants formerly in Group C and D were classified into a single group (Group E). The treatment guidance changed over time from using a long-acting bronchodilator (LABA or LAMA) for Group B participants

(based on GOLD 2019 guidance) [Singh, 2019] to using LABA/LAMA combination therapy (recommending single inhaler therapy as it may be more convenient and effective than multiple inhalers) in the GOLD 2023 guidance [Agusti, 2023b]. As the guidance had changed, it is likely that if participants in the study were evaluated presently, many participants would have been treated differently.

The study population reflects the real-world target population according to the COPD guidelines. Most participants in the study were symptomatic with a low historical exacerbation rate, prior to enrolment. Over 95% of study participants did not experience any moderate/severe COPD exacerbations in the past 12 months prior to study enrolment. Approximately half of the participants in the study had baseline mMRC scores of 0 or 1 (0: no breathlessness except on strenuous exercise, and 1: shortness of breath when hurrying on the level or walking up a slight hill), and over 20% had baseline CAT scores between 0 and 10 which indicates low impact of COPD on health.

The incidence rates of moderate/severe COPD exacerbation for UMEC, UMEC/VI, and TIO during study medication exposure period were not markedly different. Although the study was not designed nor powered to examine COPD exacerbation rates between cohorts, the preliminary study finding is consistent with a recent retrospective matched cohort study, which demonstrated no difference in KM rate of on-treatment COPD-related exacerbations between UMEC/VI and TIO [Slade, 2021]. In a post hoc analysis investigating efficacy and safety of UMEC/VI compared to TIO, the study consistently demonstrated improved lung function in UMEC/VI versus TIO [Ray, 2019]. Previous evidence had also shown that treatment with a LAMA significantly lowers the incidence of exacerbations and improves lung function [Zhang, 2021]. In addition, multiple earlier studies have demonstrated that LAMA has favorable effect on exacerbation rates compared with LABA [Decramer, 2013; Koarai, 2020; Vogelmeier, 2011].

Throughout the study period participants with more severe COPD and participants who experienced more exacerbations with their current treatment may have been more likely to switch medications. The adjusted HRs (95% CI) for medication discontinuation or switch for the UMEC and UMEC/VI cohorts compared to the TIO cohort in the FAS were 1.537 (1.374, 1.718) and 1.108 (1.000, 1.226), respectively, indicating a higher risk of discontinuation or switch among participants in the UMEC cohort. Patients not responding to UMEC may likely been switched to a dual therapy.

PSM cohort populations were used to quantify the incidence rates of stroke (all types) and hospitalization for heart failure between UMEC and UMEC/VI compared to TIO. The number of events for these outcomes were too low to draw any meaningful conclusions. Many TIO participants did not match with UMEC/VI participants which indicates these two populations were different. The low number of events may have also led to survival analysis between UMEC/VI and TIO that was underpowered.

The incidence rate of serious pneumonia/serious LRTI among UMEC/VI was numerically higher than the TIO cohort but not statistically significant (adjusted HR [95% CI]=1.185 [0.820, 1.713]). In a recent study, the risk of community-acquired pneumonia (CAP) was 4 times higher than in controls (HR 4.51, 95% CI: 4.27–4.77), independent of smoking

status, suggesting that the CAP could be due to COPD pathophysiology itself [Braeken, 2017].

Higher incidence rates of SAEs and drug-related AEs were observed in the UMEC and UMEC/VI cohorts compared to the TIO cohort. A higher incidence rate of cardiovascular and cerebrovascular AESIs were also observed in the UMEC/VI cohort than the TIO cohort. The number of certain SAEs and drug-related AEs was slightly higher in the UMEC and UMEC/VI cohorts, however the overall incidence and type of safety events observed in the study is consistent with similar studies of COPD. The incidence of SAEs, drug-related AEs, and cardiovascular and cerebrovascular AESIs were strictly monitored by the Safety team and were concluded to be aligned with the known safety profile of UMEC and UMEC/VI. The study was not powered to detect differences in SAEs, drug-related AEs, and AESIs between cohorts.

Overall, the persistence to the study medication was high across all cohorts, and no substantial difference were observed. The mean PDC between the UMEC and TIO PSM cohorts and the UMEC/VI and TIO PSM cohorts were similar. PDC estimates persistence by determining the proportion of days the participants had access to the medication over the time period, however it does not mean that participants were actually taking the medication. In a previous study, higher medication persistence (PDC ≥80%) was reported among participants initiated on UMEC/VI compared to those on TIO [Slade, 2020]. About half of participants across all cohorts had MPR of ≥80%. MPR estimates the degree of adherence to the study medication. Non-adherence to COPD medication had been previously linked to poor outcomes including increased hospitalizations, mortality, quality of life and loss of productivity among COPD patients [van Boven, 2014].

The study findings also observed lower rates of HCP visits among participants in the UMEC/VI PSM cohort due to COPD (relative rate=0.697 [95% CI=0.660, 0.736]) and all-cause visits (relative rate=0.954, [95% CI=0.929, 0.979]), and participants in the UMEC PSM cohort observed lower rates of HCP visits due to COPD (relative rate=0.797 [95% CI=0.754, 0.843]) compared to the TIO PSM cohort. The study also found lower rates of all-cause ED visits among participants in the UMEC cohort (relative rate=0.857 [95% CI=0.750, 0.978]), and lower rates of ED visits due to COPD among participants in the UMEC/VI cohort (relative rate=0.711 [95% CI=0.750, 0.978]) compared to the TIO cohort. Higher rates of all-cause hospitalization were observed for UMEC vs TIO (relative rate=1.213 [1.060, 1.389]) and UMEC/VI vs TIO (relative rate=1.210 [1.062, 1.378]). There was no difference in rates of hospitalization due to COPD in the study. A previous retrospective matched cohort study found significantly lower risk of COPD-related inpatient admission compared to TIO (rate ratio=0.80 [95% CI=0.72–0.92]) [Slade, 2020]. Although this study is a prospective study, data were collected retrospectively through participants medical charts and are prone to missing data.

## 11.4. Generalizability

The study population is presumed to be representative of the broader population of COPD participants initiating UMEC, UMEC/VI, or TIO. However, the results of this study can only be generalized to population in selected EU countries and the US. Additionally, it needs to be pointed out that participants in the study were predominantly White (>96%).

# 12. OTHER INFORMATION

## 12.1. Ethical approval and subject consent

To ensure the quality and integrity of research, this study was conducted under the Guidelines for Good Pharmacovigilance Practices (GVP) [GVP EMA Guidance] and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE) [ISPE, 2015], the Declaration of Helsinki [Declaration of Helsinki, 2008] and its amendments, and any applicable national guidelines.

### 12.1.1. Ethical approval and subject consent

Informed consent form (ICF) was signed by the participant before their participation in the study (ANNEX 1 – Informed Consent Form). The medical file for each participant documented the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF was provided to the participant. When applicable, it was provided in a certified translation of the local language. All signed and dated ICFs remained in each participant's study file and were available for verification by study monitors at any time.

The ICF was revised whenever there were changes to procedures outlined in the informed consent or when new information became available that could affect the willingness of the participant to participate. For any updated or revised ICFs, the medical file for each participant documented the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

The informed consent ensured that participants agreed to the collection of PROs at enrollment visits. All participants facing documents, including the informed consent, underwent local language translation and back translation with a qualified vendor. A translation certificate was provided for all such translations.

### 12.1.2. Subject confidentiality

Each participant was assigned a unique participant identifier upon study enrollment to maintain participant confidentiality. This participant identifier was used in place of participant names for the purpose of data analysis and reporting. Medical record numbers or other local reference identifiers were not collected as part of the study database. All parties ensured protection of participant personal data and did not include participant identifiable information on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the countries in which the study was implemented, participants were informed about data handling procedures and asked for their consent. Data protection and privacy regulations were observed in capturing, forwarding, processing, and storing participant data. Every effort was made to protect participant confidentiality according to the Regulation (EU) 2016/679 [GDPR Regulation EU 2016/679] of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and in compliance with Safe Harbor privacy principles.

The database was housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system met approved established standards for the security of health information and was validated. The system also met the standards of the International Council for Hormonisation (ICH) 2016 [ICH 2016] guideline E6R1 regarding electronic study data handling and was available for audit upon request. Participant confidentiality was strictly maintained.

## 12.2. Management and reporting of adverse events/adverse reactions

**UMEC/VI**

Adverse events from this study received by GSK were monitored individually and on an aggregate basis through GSK's routine pharmacovigilance activities.

During this study 6 signals were identified and evaluated for UMEC/VI. An evaluation for chest pain and chest discomfort in 2016 resulted in no further action. An evaluation of dysphonia, aphonia and vocal cord disorder in 2017 resulted in an update to the GSK Reference Safety Information to add dysphonia with a frequency of rare. An evaluation for dizziness in 2019 resulted in the signal being refuted. An evaluation of Drug Induced Liver Injury in 2019 which arose from a single case in a literature article for a different product, fluticasone furoate/vilanterol trifenate resulted in the signal being refuted. An evaluation of eye pain in 2021/2022 resulted in an update to the GSK Reference Safety Information to add 'Eye pain' with a frequency of rare. An evaluation of headache in 2022 resulted in an update to the GSK Reference Safety Information to add 'Headache' with a frequency of rare. All data on GSK's safety database were reviewed, including data from this study, when evaluating these signals.

**UMEC**

During this study 4 signals were identified and evaluated for UMEC. An evaluation for hypersensitivity (including rash, urticaria, pruritus, anaphylaxis, and angioedema) in 2016 resulted in an update to GSK Reference Safety Information to add 'Rash', 'Urticaria', 'Pruritus' with a frequency of uncommon and 'Anaphylaxis', 'Angioedema' with a frequency of rare. An evaluation of urinary retention and dysuria in 2017 resulted in an update to GSK Reference Safety Information to add 'Urinary retention' and 'Dysuria' with a frequency of rare. An evaluation of vision blurred, eye pain and glaucoma in 2017 resulted in an update to GSK Reference Safety Information to add 'Vision blurred', 'Glaucoma' and 'Eye pain' with a frequency of rare. An evaluation of dysphonia and oropharyngeal pain in 2022 resulted in an update to the GSK Reference Safety Information to add 'Dysphonia' and 'Oropharyngeal pain' with a frequency of rare. All data on GSK's safety database were reviewed, including data from this study, when evaluating these signals.

## 12.3. Study governance and committees

The study was conducted in close collaboration with 2 independent committees, comprised of qualified individuals with relevant experience and expertise. Each independent committee as governed by a Charter, detailing responsibilities and processes.

The composition of the Scientific Steering Committee (SSC) was 5 external members with relevant clinical and epidemiologic experience, as well as 4 GSK employees, and one representative from [redacted]. The SSC provided expert medical and epidemiological input and advice, reviewed the interim and final reports of safety data, and monitored the overall study progress through regular teleconferences and meetings. The SSC met during the protocol development and thereafter approximately every 6 months to review all interim study data and to make recommendations regarding the ongoing conduct and analysis of the study.

An EAC was implemented to adjudicate CV and cerebrovascular events of interest (specifically, MI, stroke, and heart failure and CV death) in a blinded fashion continuously throughout the study. The EAC included 4 independent medical specialists in cardiology and one neurologist who conducted a blinded review of relevant data and documentation and validated events as confirmed or unconfirmed based on a predefined algorithm. The EAC charter described a process for reconciliation of multiple independent reviews from the committee members.

# 13. CONCLUSION

In summary, the study findings presented in this report demonstrate non-inferiority to TIO for both UMEC and UMEC/VI with regards to the risk of the composite endpoint (MI, stroke, heart failure, or sudden cardiac death). The incidence rates of the composite endpoint were notably low across all cohorts, and CV mortality was also low across cohorts. There was no difference in risk of moderate/severe COPD exacerbation, consistent with previous observations. The overall benefit/risk profile for UMEC and UMEC/VI remains unchanged. While certain SAEs and drug-related AEs incidence rates were numerically greater in the UMEC and UMEC/VI cohorts compared to the TIO cohort, differences were very small. The incidence and types of safety events collected in this study, across all cohorts, were similar to other studies in COPD. The study was also not powered to detect difference for these outcomes (i.e., SAEs, drug-related AEs, and cardiovascular and cerebrovascular AESIs).

The study addressed the knowledge gap of the long-term safety risk profile of new users of UMEC and UMEC/VI compared to TIO. Results in this study provided valuable insights into the real-world safety and effectiveness for new users of UMEC and UMEC/VI compared to TIO. The study demonstrated no change in the benefit/risk profile for UMEC and UMEC/VI as treatment for patients with COPD.

# 14. REFERENCES

All references cited in this report will be made available upon request.

Agustí A, Celli BR, Criner GJ, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023a;61(4):2300239.

Agusti A, Böhm M, Celli B, et al. GOLD COPD DOCUMENT 2023: a brief update for practicing cardiologists. Clin Res Cardiol. 2023b;1-10.

Anthonisen NR, Connett JE, Enright PL, and the Lung Health Study Research Group. Hospitalisations and mortality in the lung health study. Am J Respir Crit Care Med. 2002;166:333-339.

Braeken DC, Rohde GG, Franssen FM, et al. Risk of community-acquired pneumonia in chronic obstructive pulmonary disease stratified by smoking status: a population-based cohort study in the United Kingdom. Int J Chron Obstruct Pulmon Dis. 2017;12:2425-2432.

CAT User Guide May 2022. [Internet]. Accessed on 25 July 2023.

Celli B, Crater G, Kilbride S, et al. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomised, controlled study. Chest. 2014;145(5):981-991.

Celli B, Decramer M, Leimer I, Vet al. Cardiovascular safety of tiotropium in patients with COPD. Chest. 2010;137(1):20-30.

de Luis C, Lanes SF, Jacobsen J, et al. Cardiovascular and respiratory hospitalisations and mortality among users of tiotropium in Denmark. Eur J Epidemiol. 2007;22(4):267-72.

Declaration of Helsinki 64th World Medical Association General Assembly, Seoul, October 2008 [Internet]. Accessed on 25 November 2020.

Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med. 2013;1(7):524-33.

Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med. 2014;2(6):472-86.

Donohue JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107(10):1538-46.

EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3) [Internet]. Accessed on 25 November 2020.

Fabbri LM, Luppi F, Beghé B, et al. Complex chronic comorbidities of COPD. Eur Respir J. 2008;31(1):204-12.

General Data Protection Regulation: Regulation (EU) 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC [Internet]. Accessed on 25 November 2020.

Gershon A, Croxford R, Calzavara A, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. JAMA Intern Med. 2013;173(13):1175-85.

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2017 report) [Internet]. Accessed on 20 Jul 2023.

GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report) [Internet]. Accessed on 25 May 2023.

GOLD Report - Global Initiative for Chronic Obstructive Lung Disease - GOLD (2024 report) [Internet]. Accessed on 09 Dec 2023.

Hajiro T, Nishimura K, Tsukino M, et al. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158(4):1185-9.

Hurst JR, Gruffydd-Jones K, Biswas M, et al. Efficacy and Safety of LAMA/LABA Fixed-Dose Combination Therapies in Chronic Obstructive Pulmonary Disease: A Systematic Review of Direct and Indirect Treatment Comparisons. Int J Chron Obstruct Pulmon Dis. 2020;15:1529-1543.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP E6 guideline (revision 2) date 9 November 2016. [Internet]. Accessed on 25 November 2020.

ISPE Guidelines for good pharmacoepidemiology practices (GPP) Revision 3: June 2015. [Internet]. Accessed on 25 November 2020.

Jara M, Lanes SF, Wentworth C 3rd, et al. Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database. Drug Saf. 2007;30(12):1151-60.

Jara M, Wentworth C 3rd, Lanes S. A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD. BMJ Open. 2012;2(3):e000841.

Jones P, Harding G, Wiklund I, et al. Improving the process and outcome of care in COPD: development of a standardised assessment tool. Prim Care Respir J. 2009a;18(3):208-15.

Jones PW, Harding G, Berry P, et al. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009b;34(3):648-54.

Jones PW, Harding G, Wiklund I, et al. Tests of the responsiveness of the COPD assessment test following acute exacerbation and pulmonary rehabilitation. Chest. 2012;142(1):134-140.

Koarai, A., Sugiura, H, Yamada, M, et al. Treatment with LABA versus LAMA for stable COPD: a systematic review and meta-analysis. BMC Pulm Med. 2020;20:111.

Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580-6.

Müllerova H, Agusti CoA, Erqou S, et al. Cardiovascular co-morbidity in COPD: systematic literature review. Chest. 2013;144(4):1163-1178.

Naccarelli G, Finkle J, Chopra B, et al. Cardiovascular safety of Umeclidinium/Vilanterol Coin COPD: Results from eight randomised clinical trials. Presented at the 2014 ATS Conference, May 16-21, 2014. [Internet]. Accessed on 25 November 2020.

Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ. 2016;354:i4482.

Quint, JK, Montonen J, Esposito DB, et al. Effectiveness and Safety of COPD Maintenance Therapy with Tiotropium/Olodaterol versus LABA/ICS in a US Claims Database. Adv Ther. 2021;38(5):2249–2270.

Rajala K, Lehto JT, Sutinen E, et al. mMRC dyspnoea scale indicates impaired quality of life and increased pain in patients with idiopathic pulmonary fibrosis. ERJ Open Res. 2017;3(4):00084-2017.

Ray R, Tombs L, Naya I, et al. Efficacy and safety of the dual bronchodilator combination umeclidinium/vilanterol in COPD by age and airflow limitation severity: A pooled post hoc analysis of seven clinical trials. Pulm Pharmacol Ther. 2019;57:101802.

Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003;158(9):915-20.

Rebordosa C, Plana E, Rubino A, et al. Risk Assessment of Acute Myocardial Infarction and Stroke Associated with Long-Acting Muscarinic Antagonists, Alone or in Combination, versus Long-Acting beta2-Agonists. Int J Chron Obstruct Pulmon Dis. 2022;17:1715-1733.

Requena G, Dedman D, Quint JK, et al. The Utilization and Safety of Umeclidinium and Umeclidinium/Vilanterol in UK Primary Care: A Retrospective Cohort Study. Int J Chron Obstruct Pulmon Dis. 2021;16:629-642.

Rosenbaum PR, Rubin DR. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70 (1):41-55.

Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest. 2004;125(6):2309-21.

Singh S, Loke YK, Enright PL, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive polumonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ. 2011;342:d3215.

Singh S, Loke YK, Enright PL, et al. Pro-arrhythmic and pro-ischaemic events of inhaled anticholinergic medications. Thorax. 2013;68(1):114-6.

Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(12):1439-50.

Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53:1900164.

Slade D, Ray R, Moretz C, et al. Medication adherence and copd-related costs among patients with copd treated with umeclidinium/vilanterol (UMEC/VI) vs tiotropium (TIO). Chest. 2020;158(4):A1720-A1721.

Slade D, Ray R, Moretz C, et al. Time-to-first exacerbation, adherence, and medical costs among US patients receiving umeclidinium/vilanterol or tiotropium as initial maintenance therapy for chronic obstructive pulmonary disease: a retrospective cohort study. BMC Pulm Med. 2021;21(1):253.

Stürmer T, Joshi M, Glynn RJ, et al. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol. 2006;59(5):437-47.

Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543-54.

Tamondong-Lachica DR, Skolnik N, Hurst JR, et al. GOLD 2023 Update: Implications for Clinical Practice. Int J Chron Obstruct Pulmon Dis. 2023;18:745-754.

Vaduganathan M, Mensah GA, Turco JV, et al. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. J Am Coll Cardiol. 2022;80(25):2361-2371.

van Boven JF, Chavannes NH, van der Molen T, et al. Clinical and economic impact of non-adherence in COPD: a systematic review. Respir Med. 2014;108(1):103-13.

Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12):1093-1103.

Vogelmeier CF, Kerwin EM, Bjermer LH, et al. Impact of baseline COPD symptom severity on the benefit from dual versus mono-bronchodilators: an analysis of the EMAX randomised controlled trial. Ther Adv Respir Dis. 2020;14:1753466620968500.

World Health Organisation (WHO). The top 10 causes of death dated 09 December 2020. [Internet]. Accessed on 11 May 2023.

Zannad F, Huvelle E, Dickstein K, et al. Left bundle branch block as a risk factor for progression to heart failure. Eur J Heart Fail. 2007;9(1):7-14.

Zhang C, Zhang M, Wang Y, et al. Efficacy and cardiovascular safety of LAMA in patients with COPD: a systematic review and meta-analysis. J Investig Med. 2021;69(8):1391-1398.