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Randomized controlled trials and real-world observational studies in evaluating cardiovascular safety of inhaled bronchodilator therapy in COPD

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Abstract: Long-acting muscarinic antagonist (LAMA) or long-acting β2-agonist (LABA) bronchodilators and their combination are recommended for the maintenance treatment of chronic obstructive pulmonary disease (COPD). Although the efficacy of LAMAs and LABAs has been well established through randomized controlled trials (RCTs), questions remain regarding their cardiovascular (CV) safety. Furthermore, while the safety of LAMA and LABA monotherapy has been extensively studied, data are lacking for LAMA/LABA combination therapy, and the majority of the studies that have reported on the CV safety of LAMA/LABA combination therapy were not specifically designed to assess this. Evaluation of CV safety for COPD treatments is important because many patients with COPD have underlying CV comorbidities. However, severe CV and other comorbidities are often exclusion criteria for RCTs, contributing to a lack in external validity and generalizability. Real-world observational studies are another important tool to evaluate the effectiveness and safety of COPD therapies in a broader population of patients and can improve upon the external validity limitations of RCTs. We examine what is already known regarding the CV and cerebrovascular safety of LAMA/LABA combination therapy from RCTs and real-world observational studies, and explore the advantages and limitations of data derived from each study type. We also describe an ongoing prospective, observational, comparative post-authorization safety study of a LAMA/LABA combination therapy (umeclidinium/vilanterol) and LAMA monotherapy (umeclidinium) versus tiotropium, with a focus on the relative merits of the study design.

Keywords: real-world observational study, cardiovascular, cerebrovascular, safety, umeclidinium, vilanterol

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, accounting for approximately three million deaths worldwide in 2012.[1,2] As COPD is characterized by persistent airflow limitation, long-acting muscarinic antagonists (LAMA) or long-acting β2-agonist (LABA) bronchodilators are recommended treatment options.[1] Bronchodilator monotherapy with LAMAs improves lung function and health status, and prevents exacerbations compared with placebo.[3–5] Combination therapy with LAMAs and LABAs exert complementary bronchodilatory effects, resulting in greater improvements in lung function compared with long-acting bronchodilator monotherapies.[4,6–10] These dual combination bronchodilators also improve symptoms and health status, and reduce exacerbation risk to a greater extent than monotherapies or inhaled corticosteroid/LABA combinations.[6,7,10,11]

Due to their mechanisms of action, both LAMAs and LABAs have the potential to cause cardiac-related adverse events (AEs). LAMAs suppress parasympathetic control of heart rate (HR) and LABAs stimulate sympathetic control of HR. These effects serve to raise HR with the potential to cause cardiac arrhythmias, myocardial infarction (MI), stroke, and sudden death in susceptible patients.[1,12–15] When administered as combination therapy, LAMAs and LABAs are often combined using the same doses as for monotherapy. Thus, hypothetically, an increase in cardiovascular (CV) AEs compared with monotherapy cannot be excluded.

Randomized controlled trials (RCTs) are considered the gold standard study design for gaining evidence for regulatory approval. Real-world observational studies are often non-interventional in nature and may be prospective or retrospective in design. They are conducted in wider patient populations who have a range of demographics and characteristics and are important for monitoring the effects of therapies outside of the controlled setting. This is particularly important in COPD, where CV comorbidities are prevalent,[16] but are frequently an exclusion criterion for participation in RCTs,[17–20] an issue that has been coined the "COPD trial paradox".[12] Here, we review the available evidence from RCTs and real-world observational studies regarding the CV and cerebrovascular safety of LAMA/LABA combination therapy versus monotherapy in COPD. We also include a special focus on an ongoing prospective, observational, comparative post-authorization safety (PAS) study of the LAMA/LABA combination therapy, umeclidinium (UMEC)/ vilanterol (VI), or UMEC monotherapy versus the LAMA monotherapy, tiotropium (TIO).

Evidence from COPD RCTs

Although the CV and cerebrovascular risk of LAMA and LABA monotherapies have been extensively examined in RCTs, relatively few studies have reported on the safety of LAMA/LABA combination therapies. RCTs that have reported on the CV and cerebrovascular safety of LAMA/ LABA combination therapy are described in Table 1. Furthermore, the studies that do report on the CV and cerebrovascular safety of LAMA/LABA combinations were not necessarily powered to study these outcomes, with the exception of Van de Maele et al[21] the primary outcome of which was change from baseline in 24-h mean HR. Overall, the available evidence from RCTs has not shown any clinically significant increase in CV or cerebrovascular risk for the LAMA/LABA combinations UMEC/VI,[5,7,8,10,22–26] TIO/olodaterol,[17,27,28] aclidinium/ formoterol,[29,30] or indacaterol/glycopyrronium[6,21,31–33] versus

Table 1 RCTs reporting on the CV and cerebrovascular safety of LAMA/LABA combination therapy

Reference	N trial participants	Treatment arms	Safety outcomes assessed	CV and cerebrovascular outcomes
UMEC/VI				
Celli et al (2014)[5]	1,493 randomized; 1,489 in ITT	UMEC/VI 125/25 µg; UMEC 125 µg; VI 25 µg; placebo	AEs, vital signs, 12-lead ECG, 24-h Holter ECG, clinical chemistry, and hematology assessments	No clinically meaningful changes in vital signs, ECG assessments (including 12-lead and Holter recordings), and clinical laboratory tests were observed for UMEC/VI, UMEC, or VI compared with placebo
Naccarelli et al (2014)[24]	6,156 in the MACE analysis; 5,295 in the CV AESIs analysis	Pooled analysis of 8 RCTs of: UMEC/VI 125/25 µg; UMEC/ VI 62.5/25 µg; UMEC 62.5 µg; UMEC 125 µg; VI 25 µg; or active-comparator (TIO)	Broad MACE analysis included MedDRA preferred terms for "MI", and "Other ischemic heart disease". Narrow MACE specified "acute MI" and "MI only"; both analyses also included adjudicated CV death and nonfatal stroke CV AESIs: acquired long QT interval, cardiac arrhythmias, cardiac failure, cardiac ischemia, hypertension, sudden death, and stroke	No clinically relevant increase in CV events was observed with UMEC/VI, UMEC, or VI compared with placebo
Maltais et al (2014)[23]	Study 1: 308 randomized; 307 patients in ITT population Study 2: 349 randomized; 348 in ITT population	UMEC/VI 125/25 µg; UMEC/ VI 62.5/25 µg; VI 25 µg; UMEC 62.5 µg; UMEC 125 µg; placebo	AEs, exacerbations, vital signs, clinical chemistry parameters, hematology parameters, and 12-lead ECGs	Proportion of patients with abnormal, clinically significant ECG assessments was similar across all treatments

Siler et al (2015)[25]	Study 1: 619 randomized and in ITT population Study 2: 620 randomized; 619 in ITT population	UMEC 62.5 mg; UMEC 125 mg; placebo (added to open-label fluticasone furoate (FF)/VI)	AEs, vital signs (pulse rate and systolic and diastolic BP), exacerbations, and AESIs (CV events, pneumonia, and lower respiratory tract infections)	Incidence of CV AESIs was low and similar across all treatment groups
Hu et al (2015)[22]	20 randomized	UMEC/VI 62.5/25 μg; UMEC/VI 125/25 μg; UMEC 62.5 μg; UMEC 125 μg; VI 25 μg	AEs, SAEs, vital signs (systolic and diastolic BP and HR), 12-lead ECG, maximum 0–4 h QTcF, maximum 0–4 h HR, 0–4 h weighted mean QTcF and 0–4 h weighted mean HR, clinical chemistry, hematology, and urinalysis	No clinically important changes in vital signs, HR, or ECG parameters were observed for each treatment group
Decramer et al (2014)[7]	Study 1: 846 randomized; 843 in ITT population Study 2: 872 randomized; 869 in ITT population	UMEC/VI 125/25 μg; UMEC/VI 62.5/25 μg; TIO 18 μg; VI 25 μg (Study 1); UMEC 125 μg (Study 2)	AEs, SAEs, vital signs, ECG, and laboratory data	No notable difference in BP, HR, or QT interval observed between treatment groups in either study, and no treatment-related changes in ECG parameters
Maleki-Yazdi et al (2014)[10]	905 randomized and in ITT population	UMEC/VI 62.5/25 μg; TIO 18 μg	AEs, SAEs, and AESIs (CV events, pneumonia, and lower respiratory tract infections)	Incidence of CV AESIs was equivalent between UMEC/VI 62.5/25 μg and TIO 18 μg
Donohue et al (2014)[8]	563 randomized; 562 in ITT population	UMEC/VI 125/25 μg; UMEC 125 μg; placebo	AEs, vital signs, clinical chemistry, hematology, 12-lead ECG, 24-h Holter ECG, and AESIs (CV effects, effects on glucose and potassium, tremor, urinary retention, ocular effects, gallbladder disorders, intestinal obstruction, and anticholinergic effects)	Lower overall incidence of CV AEs with UMEC/VI than UMEC or placebo Proportion of patients with one or more abnormal, clinically significant 12-lead ECG interpretation or with one or more abnormal, clinically significant Holter ECG interpretation similar across all treatment groups Incidence of atrial arrhythmias with UMEC/VI similar to placebo, but some arrhythmias had a ≥2% greater incidence with UMEC compared with placebo No clinically relevant differences in QTc interval, PR interval, or HR observed between treatments
Donohue et al (2016)[26]	Study 1: 207 randomized and in ITT population Study 2: 182 randomized and in ITT population	UMEC/VI 62.5/25 μg; UMEC 62.5 μg; VI 25 μg	AEs, vital signs, and COPD exacerbations; Study 2 only: 12-lead ECGs, and clinical laboratory tests (hematology and clinical chemistry)	No clinically significant changes in QT interval (corrected for HR by Bazett's and Fridericia's formulae), PR interval, HR, or changes in these parameters from baseline observed Six patients were withdrawn due to ECG abnormalities (UMEC/VI: 4; UMEC: 1; VI: 1)
TIO/olodaterol			
Singh et al (2015)[27]	Study 1: 814 randomized; 812 treated; Study 2: 809 randomized and treated	TIO/olodaterol 5/5 μg; TIO/olodaterol 2.5/5 μg; TIO 5 μg; placebo	AEs, SAEs, vital signs, and 12-lead ECG	Incidences of AEs in the "cardiac disorders" Systems Organ Class were similar across treatments
ZuWallack et al (2014)[28]	Study 1: 1,134 randomized; 1,132 treated; Study 2: 1,137 randomized; 1,135 treated	TIO/Olodaterol 18/5 μg; TIO 18 μg + placebo	AEs, SAEs, vital signs, blood chemistry, and ECG	No changes in laboratory parameters, vital signs, or ECG were indicative of a safety signal

(Continued)

Table 1 (*Continued*)

Reference	N trial participants	Treatment arms	Safety outcomes assessed	CV and cerebrovascular outcomes
Buhl et al (2015)[17]	Study 1: 2,624 randomized and treated; Study 2: 2,539 randomized; 2,538 treated	TIO/olodaterol 2.5/5 µg; TIO/olodaterol 5/5 µg; TIO 2.5 µg; TIO 5 µg; olodaterol 5 µg	AEs, SAEs, vital signs, laboratory parameters, and MACE (in subset of patients with cardiac history)	The incidences of MACE were similar with TIO/olodaterol and individual components
Aclidinium/formoterol				
Singh et al (2014)[30]	1,729 in safety analysis set	Aclidinium/formoterol 400/12 µg; aclidinium/formoterol 400/6 µg; aclidinium 400 µg; formoterol 12 µg; placebo	AEs, laboratory tests, BP, 12-lead ECG, 24-h 12-lead Holter recordings, and MACE (a composite of total CV death, nonfatal MI, and nonfatal stroke)	The incidence of MACE was low and comparable across all groups. There were no clinically significant differences between treatment groups in clinical laboratory tests, vital signs, and ECGs (including 24-h or 12-lead Holter recordings)
D'Urzo et al (2014)[29]	1,692 randomized; 1,668 in ITT population	Aclidinium/formoterol 400/12 µg; aclidinium/formoterol 400/6 µg; aclidinium 400 µg; formoterol 12 µg; placebo	AEs, clinical laboratory tests, vital signs, ECGs, 24-h 12-lead Holter monitoring, and MACE (composite of CV deaths, nonfatal MIs, and nonfatal strokes)	Number of MACEs were infrequent and occurred at similar incidences across all treatment groups. Holter monitoring did not show any findings of an ECG effect for patients in any group, and no differences were observed between treatments
Indacaterol/glycopyrronium				
Mahler et al (2014)[31]	247 randomized	Indacaterol/glycopyrronium 110/50 µg; TIO 18 µg; placebo	AEs, SAEs, physical examinations, laboratory assessments, ECGs, and vital signs	The incidence of SAEs was similar across groups and serious CV and cerebrovascular AEs were infrequent. One death (left ventricular failure leading to cardiac arrest) occurred in the indacaterol/glycopyrronium group
Van de Maele et al (2010)[21]	257 randomized	Indacaterol/glycopyrronium 600/100 µg; indacaterol/glycopyrronium 300/100 µg; indacaterol/glycopyrronium 150/100 µg; Indacaterol 300 µg; Placebo	Primary endpoint: change from baseline in 24-h mean HR versus placebo on day 14	No clinically significant differences in the 24-h mean HR between the three doses of indacaterol/glycopyrronium and placebo or indacaterol. No clinically relevant differences in QTc interval (Fridericia's) between groups
Bateman et al (2013)[6]	2,144 randomized	Indacaterol/glycopyrronium 110/50 µg; indacaterol 150 µg; glycopyrronium 50 µg; TIO 18 µg; placebo	AEs, SAEs, ECGs, hematology, clinical chemistry, urinalysis, physical condition, and vital signs (pulse and BP). 24-h Holter monitoring in a subset of patients	No serious CV and cerebrovascular events in the indacaterol/glycopyrronium group and few reported and adjudicated in the other treatment groups. Atrial fibrillation/flutter events (ie, reported as AEs, SAEs, or ECG findings) were uncommon in all groups. No clinically relevant differences in QTc interval (Fridericia's formula) between treatment groups
Wedzicha et al (2014)[32]	11,404 pooled from 14 RCTs	Indacaterol/glycopyrronium 110/50 µg; glycopyrronium 50 µg; indacaterol 150 µg; TIO 18 µg; placebo	All-cause mortality, CV, cerebrovascular events, and MACE (nonfatal MI, unstable angina, nonfatal stroke, heart failure, and coronary revascularization)	No significant increase in overall risk for serious CV and cerebrovascular events, MACEs, or atrial flutter/fibrillation for indacaterol/glycopyrronium versus placebo. No significant increase in risk for indacaterol/glycopyrronium versus placebo for any of the CV safety endpoints for all subgroup analyses based on COPD severity, baseline ICS use, CV risk factors, sex, age, or BMI. Risk was comparable to those for TIO versus placebo

Mahler et al (2015)[33]	2,038 pooled from 2 RCTs	Indacaterol/glycopyrrolate (27.5/15.6 µg twice daily); indacaterol 27.5 µg twice daily; glycopyrrolate 15.6 µg twice daily; placebo	AEs, SAEs, CV, cerebrovascular AEs, SAEs, and MACE	Incidence of CV and cerebrovascular AEs and MACE was comparable across treatments
Patients with at least one CV and cerebrovascular SAE were comparable across treatments

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ECG, electrocardiogram; HR, heart rate; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; RCT, randomized controlled trial; SAE, serious adverse event; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

monotherapy or placebo (Table 1). Indeed, one study reported that the incidence of atrial arrhythmias was similar between UMEC/VI 125/25 µg and placebo, but had a ≥2% greater incidence with UMEC 125 µg compared with placebo. Additionally, the overall incidence of CV AEs with UMEC/VI 125/25 µg was lower compared with UMEC 125 µg or placebo, although because the event rate was low and the study not powered to detect these treatment differences in this endpoint, these results should be interpreted with caution.[8]

Advantages and limitations of COPD RCTs

RCTs typically have high internal validity due to the random allocation of patients to treatment groups, minimizing indication bias and confounding, as well as reducing biased reporting of endpoints. Additionally, a placebo/control arm can be used to measure the impact and remove any imbalance of the patient- and investigator-related Hawthorne effects (the phenomenon where individuals modify or improve aspects of their behavior in response to being observed)[34] across treatment arms. The use of precise inclusion and exclusion criteria in RCTs also minimizes the effect of confounding factors such as patient comorbidities.[35] However, exclusion criteria are used to exclude high-risk patients. For example, the TIOtropium Safety and Performance In Respimat (TIO-SPIR) safety study targeting comorbid patients excluded the highest risk patients, such as those with previous MI, New York Heart Association class III or IV heart failure, or unstable or life-threatening arrhythmia.[36] The high internal validity of RCTs allows treatment effects to be reliably determined. Consequently, RCTs are considered the gold standard for evaluating the efficacy of novel therapies to obtain regulatory approval.[37]

However, trial results need to be generalizable and suitable for extrapolation to a wider patient population to be clinically useful. There are several reasons why RCTs in COPD have often lacked external validity. COPD studies often enforce exclusion criteria based on age (an upper age limit of 70–75 years is common), disease severity (often excluding patients with mild airflow and very severe obstruction; forced expiratory volume in 1 second [FEV_1] >80% predicted and <30% predicted, respectively), comorbid conditions that potentially cause excessive risk for AEs, background maintenance therapy use, or long-term oxygen therapy.[38] The resulting patient populations are homogeneous but less generalizable to the wider heterogeneous COPD patient population.[39,40]

COPD has an established association with CV and other comorbidities. For example, 98% of patients with COPD in a

secondary care referral study had ≥1 comorbid condition and over half had ≥4 comorbid conditions.[41] Although common in the general COPD patient population, such comorbidities are frequently exclusion criteria in RCTs.[12,17–20,35] Thus, there is a mismatch between a real-life COPD patient population and the subset of patients that would fit into the criteria used by RCTs.[42–45] A postal survey was conducted in 2002–2005 in patients with COPD in New Zealand to determine eligibility for inclusion in any one of 18 previously conducted RCTs cited in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The study found that eligibility ranged from 0% to 20% in all subjects with COPD and from 0% to 9% in those patients receiving treatment for COPD with inhaled or oral steroids, or bronchodilators. These results demonstrate that the external validity of the major RCTs on which the GOLD treatment guidelines was based is low.[46] Similarly, two other analyses each demonstrated that just 17% of a real-life COPD patient population would fit the criteria commonly used in RCTs in COPD.[42,44]

More recently, Kruis et al[45] evaluated the external validity of six large industry-sponsored COPD trials (ISOLDE, TRISTAN, TORCH, UPLIFT, ECLIPSE, and POET-COPD), on which current COPD treatment guidelines are largely based. Compared with data from seven large European primary care databases, the population included in these RCTs was younger, predominantly male, with worse lung function and poorer quality of life. There was also a large difference in the disease severity (GOLD) distribution of patients enrolled in the RCTs versus the primary care database. For example, no patients with COPD with mild severity (GOLD I) were included in the RCTs, while patients with severe COPD (GOLD III) were overrepresented in the industry-sponsored studies versus the primary care population (44.5% vs 21%, respectively). Furthermore, baseline data on exacerbations suggested overrepresentation of patients with prior exacerbations in the RCTs compared with the primary care population. Overall, it was shown that the proportion of patients from the primary care population that would be eligible to be included in the industry-sponsored RCTs ranged from 17% (TRISTAN) to 42% (ECLIPSE and UPLIFT).

Other factors that impact the external validity of RCTs relate to the trial setting (primary, secondary, or tertiary care), the health care system, and the country in which the trial is conducted.[35] Even where health care systems are similar, other differences such as racial demographics, disease susceptibility, and natural history of the disease can influence external validity.[35] Furthermore, differences between health care systems can affect hospital admissions, a factor that defines a COPD exacerbation as severe. However, the threshold for hospitalization differs between countries. For example, an adjusted 10-fold difference in respiratory disease-related hospital admissions has been reported across 31 European countries, being highest in Eastern Europe and Germany, and lowest in France, Portugal, UK, and Scandinavia.[47]

Evidence from COPD real-world observational studies

Data from real-world observational studies reporting on LAMA/LABA combination therapy in COPD are currently lacking. Recently, a real-world study of patients included in the Registre de Données en Santé Pulmonaire database, which records information on Canadian patients with asthma or COPD, compared AEs associated with LAMA or LABA monotherapy use and LAMA/LABA combination use in patients with COPD. However, the study did not specifically report on CV and cerebrovascular AEs.[48] Indeed, to date, we are not aware of any real-world observational studies that have specifically assessed the CV and cerebrovascular risk of LAMA/LABA combination therapy in COPD.

Advantages and limitations of COPD real-world observational studies

Real-world observational studies are designed to more closely reflect routine clinical practice and thus do not exclude patients with comorbidities associated with COPD or have further limitations with inclusion criteria such as upper age limit or smoking history. In contrast to RCTs, observational studies include a wider selection of patients and focus on balancing the risks and benefits of treatments.[37] In contrast to the internal validity achieved in RCTs, the main advantage of real-world observational studies is their higher external validity, generally enrolling a wide range of patients across different treatment settings.[34,37] Real-world data from observational studies can also provide evidence of effectiveness to support health care decisions[49] and assist health care policy makers in dealing with coverage and reimbursement decisions when evaluating the cost effectiveness of a treatment.[50,51] Real-world observational studies also ensure that drug safety is monitored in a broad population of patients.

Prospective non-interventional studies, such as DAC-CORD registry, or the open-label pragmatic trial called the Salford Lung Study are examples of large observational COPD studies generating real-world evidence.[49,52] DACCORD is an ongoing 2- to 4-year real-world study being conducted in over 6,000 patients in ~500 primary and secondary care practices in Germany. Patients fall into two groups, one treated according to standard of care with a glycopyrronium-containing regimen and another group

treated according to standard of care without glycopyrronium. The study focuses on patient-related outcomes, time to first exacerbation, frequency of exacerbations, and lung function variables. The main strengths of the DACCORD study are the large size of study population, the long-term follow-up period, the broad inclusion criteria, and the implementation of disease management program criteria, which aims to ensure that only patients with appropriate COPD diagnosis are enrolled.[52] The Salford Lung Study consists of two open-label Phase III pragmatic RCTs in asthma and COPD. It was designed to compare the real-world effectiveness of fluticasone furoate/VI via inhaler (plus standard care) versus regular maintenance therapy (plus standard care) for COPD and asthma in routine primary care. Following randomization, patients receive standard care by their physician for 12 months and effectiveness and safety data were collected using electronic health records. The design strengths of the Salford Lung Study are that it is a large, prospective, randomized study with broad inclusion criteria, which allow it to bridge the gap between low external validity RCTs and low internal validity non-randomized observational studies.[49,53] One potential limitation of the study is the relatively high level of intervention required by regulatory authorities due to the randomized nature of the trial, as this undermines the real-world design of the study, impacting on the Hawthorne effect.

The main limitations with real-world studies, specifically observational studies (ie, without random subject allocation), are the effects of potential confounding by indication bias, where the most severe patients may preferentially receive certain treatments.[39] Additionally, the lack of blinding in real-world studies is generally considered a limitation. However, this reflects clinical practice where patients either receive treatment or nothing at all. Thus, the efficacy of treatment versus placebo, already proven in completed RCTs, is not the target outcome of observational studies. If a comparator intervention already exists, then the usual standard of care may be a more appropriate comparator.[37] Observational studies that are retrospective in nature use electronic records and these studies can be limited by the robustness and completeness of their data sources, such as inconsistent reporting of data on disease severity. Another important source of bias in real-world observational studies is attrition bias. For example, in the DACCORD study, of the 6,000 patients initially included in the study, only 4,123 patients remained after 1 year.[54]

A PAS study of UMEC/VI combination therapy

There are a few studies with large patient populations that have specifically assessed the CV and cerebrovascular safety of LAMAs and LABAs, such as SUMMIT, TORCH, UPLIFT, and TIOSPIR.[36,55–57] However, much of the available data assessing CV and cerebrovascular risk have come from non-prespecified AE analyses in RCTs, which may not have been powered for CV AEs.

The 201038 PAS study is a prospective real-world observational cohort study that aims to reflect the real-world experience of patients with COPD treated with UMEC/VI or UMEC in the post-approval setting. The primary objectives of the study are to demonstrate the non-inferiority of UMEC/VI and UMEC alone versus TIO for the risks of MI, stroke, or heart failure, each based on an analysis of time to first event. The study will also quantify the incidence rate and frequency of MI, stroke, and heart failure for new users of UMEC/VI, UMEC, and TIO. The primary and secondary safety outcomes are presented in Table 2.

Study design

This study is a non-randomized, observational study being carried out in several European Union (EU) and non-EU countries that have UMEC/VI, UMEC, and TIO available on prescription. Patients are enrolled in the study at the time of receiving a new prescription for UMEC/VI, UMEC, or TIO. The decision to initiate treatment with UMEC/VI, UMEC, or TIO is made independently by the patient and their physician and is not mandated by the study design or protocol. All patients are followed from initiation of treatment until the required number of CV events has been observed in the study population. All patients are observed over a minimum of 24 months, or until withdrawal of consent, loss to follow-up, or death (Figure 1). The estimated maximum duration of follow-up is between 2 and 5 years. Data on patients are collected at routine visits at least twice yearly, as well as at unscheduled visits as per normal standard of care. All data will be collected via electronic case report forms (eCRFs) from information routinely recorded in patient's medical records or through patient self-report. Hospital discharge summaries will be requested by the investigator or site staff for all hospitalizations of enrolled patients. Data from these summaries will be captured on the eCRF and also used for adjudication of CV and cerebrovascular events. Written, informed consent was and will be obtained from all patients who participate in the study. The study was approved by Sächsische Landesärztekammer, Dresden, Germany and other relevant national, regional, or investigational center Ethics Committee/Institutional Review Boards, and is and will be performed in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good

Table 2 Primary and secondary study safety outcomes in the 201038 Post-authorization Safety Study of UMEC/VI combination therapy

Primary study safety outcomes	Secondary study safety outcomes
Time to first event of each of MI, stroke, and heart failure (new or acute worsening)	Time to first composite safety endpoint (MI, stroke, heart failure, or sudden cardiac death)
Incidence rate[a] of each of MI, stroke, and heart failure (new or acute worsening)	Incidence rate[a] of composite safety endpoint (MI, stroke, heart failure, or sudden cardiac death)
Total number of events of each of MI, stroke, and heart failure (new or acute worsening)	Incidence rate[a] and total number events of hemorrhagic stroke, ischemic stroke, undefined stroke, and hospitalization for heart failure
	Incidence rate[a] of serious pneumonia/LRTI
	Total number of events and event rate of all pneumonia/LRTI AEs
	Mortality rate (all-cause, CV-related, and non-CV-related)
	CV AEs of special interest[b], drug-related AEs, all SAEs[c], and all deaths

Notes: [a]Per person year; [b]including transient ischemic attacks, angina, cardiac arrhythmias, acquired long-QT interval, cardiac ischemia and hypertension; [c]according to MedDRA SOC and PT; All treatment comparisons of primary and secondary safety outcomes will be analyzed using hazard ratios for time to first event.
Abbreviations: AE, adverse event; CV, cardiovascular; LRTI, lower respiratory tract infection; MedDRA, medical dictionary for regulatory activities; MI, myocardial infarction; PT, preferred term; SAE, serious adverse event; SOC, system organ class; UMEC, umeclidinium; VI, vilanterol.

Clinical Practice (ICH-GCP) guidelines and all applicable patient privacy requirements and the ethical principles outlined in the Declaration of Helsinki, 2013.

Study population

The study is enrolling ~7,800 patients from 700 study centers in selected EU member states and other non-EU countries where UMEC/VI, UMEC, and TIO are available on prescription. Enrollment in non-EU countries is capped at ~50%. Eligible patients are enrolled by primary care physicians and pulmonologists and are aged ≥18 years, with a clinical diagnosis of COPD verified by spirometry (defined as a post-bronchodilator FEV_1/forced vital capacity ratio of <0.7) and initiating treatment with either UMEC/VI, UMEC, or TIO. Key exclusion criteria include current participation in any interventional clinical trials; hypersensitivity to UMEC, VI, TIO, or excipients; and maintenance

treatment (defined as ≥60 days of continuous use) with a LAMA-containing medication during the 12 months prior to enrollment. At enrollment, detailed data on patient demographics, baseline characteristics, modified Medical Research Council and COPD assessment test questionnaire scores, disease comorbidities, and concomitant medication use are collected using an eCRF. Information is provided by the treating physician based on a combination of self-reported information from the enrolled patient and where available, supplemented by the patient's electronic medical records. The study is event-driven, requiring at least 98 events for each of MI, stroke, and heart failure for each pair of treatments (UMEC/VI vs TIO; UMEC vs TIO). Therefore, the number of patients that need to be enrolled will be updated as necessary throughout the study. The study has a 90% power to reject a non-inferiority margin of a hazard ratio of 2.0 for each treatment pair for each outcome (MI, stroke, and heart failure). This is based on the requirement that the 95% confidence interval for the hazard ratio excludes 2.0.

Advantages and limitations of the study design

The study incorporates several important design features that aim to minimize the potential limitations of observational studies, such as potential confounding by indication bias or attrition bias, and the lack of blinding. Observational studies are often retrospective; however, enrollment in this study is prospective, allowing for robust data collection through eCRFs. The study aims to recruit a wide population of patients with COPD from different care settings. Eligible patients are enrolled by both primary care physicians and pulmonologists, which helps to ensure representation from different care settings. Patients "new" to therapy are defined as not having received LAMA maintenance therapy for ≥60 consecutive days during the
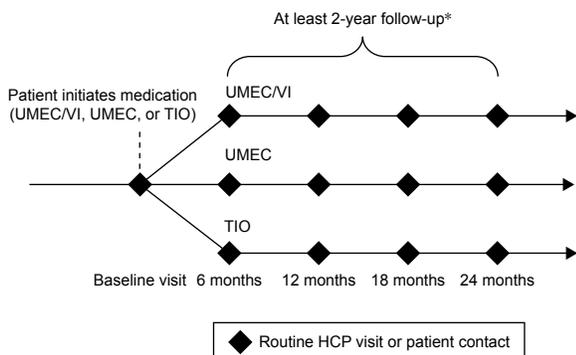
Figure 1 Study design for the new 201038 Post-authorization Safety Study of UMEC/VI combination therapy.
Note: *The follow-up period will be defined as the period between the prescription index date until the earliest of: date when the planned number of events has been reached, 14 days following date of discontinuation of initiated COPD medication, withdrawal from the study, conclusion of study follow-up or death.
Abbreviations: COPD, chronic obstructive pulmonary disease; HCP, health care practitioner; TIO, tiotropium; VI, vilanterol; UMEC, umeclidinium.

previous 12 months. This should minimize enrolled patient "survival" bias, where prevalent users of LAMAs that have survived are disproportionately represented in any treatment groups.[58] This is particularly important for assessing whether mortality risk is affected by treatment. Specifically, it minimizes the bias of prescription of two LAMAs (eg, UMEC/VI added to TIO), which may unfortunately occur in error. However, this is also a potential limitation of the study as it excludes many patients, particularly as LAMA maintenance is the most frequently prescribed treatment for COPD in some countries, such as Germany.[59] The requirement that patients must not have received LAMA maintenance therapy for ≥60 consecutive days during the prior 12 months also limits the patients included, meaning that the enrolled population will not be fully representative of the wider COPD patient population. However, patients can continue on existing maintenance treatments, which helps to reduce the potential for excluding patients with more severe disease. Also the factors that may be associated with treatment choice (and with risk of primary events) are documented to account for potential confounding in propensity score analyses. Additionally, as follow-up does not require patients to return to their study center except for routine care, follow-up bias whereby patients with AEs are more or less likely to return to see their study physician is minimized by maintaining a low lost to follow-up rate (a rate of <5% is anticipated). Furthermore, to standardize the reporting of primary CV events (MI, stroke, or heart failure) between centers (which may adopt different interpretations and event definitions), only events confirmed by the blinded adjudication committee are included. The expected event rates for MI, stroke, and heart failure are 98, 108, and 168,[60] although as the study is event-driven, recruitment rates will be adjusted once the actual event rate in this population is known.

Conclusion

Both RCTs and real-world observational studies contribute important data regarding the efficacy, safety, and effectiveness of COPD treatments. When evaluating a treatment effect it is important for health care practitioners to consider the generalizability of study findings to their patients. As both study types have inherent limitations, data from the pivotal COPD RCTs are complemented by real-world observational study data, which should both be evaluated to elucidate evidence of any treatment benefits and safety concerns. More research is needed to determine the effects of COPD treatments in patients who have been underrepresented in RCTs, such as women and patients with mild and very severe disease. Furthermore, the CV safety of COPD treatments in real-life patients, including those with comorbidities, should be further investigated, both in observational studies and more inclusive pragmatic RCTs. As there is hypothetically a potential for higher CV risk with dual bronchodilator treatment, the new 201038 PAS study documented here will provide data on the CV and cerebrovascular risks of the LAMA/LABA combination UMEC/VI, and the LAMA monotherapies UMEC and TIO in a real-world setting. The study design aims to reduce some of the common limitations of observational studies and to provide safety data for dual bronchodilator therapy in a more vulnerable COPD population than those included in RCTs.

Author contributions

PK, SW, DS, MR-R, HM, and DEN contributed to the study concept and design. All authors were involved in the preparation and review of the manuscript, approved the final version submitted and agree to be accountable for all aspects of the work.

Disclosure

DEN has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including AstraZeneca, BMS, Boehringer Ingelheim, GSK, Novartis, and Pfizer.

DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Genentech, GSK, Glenmark, Johnson & Johnson, Merck, NAPP, Novartis, Pfizer, Skyepharma, Takeda, Teva, Theravance, and Verona.

MR-R has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from various pharmaceutical companies including Almirall, AstraZeneca, Boehringer

Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Pfizer, ROVI, and Teva.

PK received honoraria for lecturing and advisory boards from the following pharmaceutical companies: AstraZeneca, Boehringer Ingelheim, Chiesi, Menarini, Mundipharma, Novartis, Roche, Takeda, and Teva; and sponsorship for German national and international conferences from AstraZeneca, Boehringer Ingelheim, Menarini, and Novartis.

SW and HM are employees of GSK and hold stocks/ shares in GSK.

The authors report no other conflicts of interest in this work.

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