InforMing the PAthway of COPD Treatment (IMPACT trial)-Single Inhaler Triple Therapy (FF/UMEC/VI) Versus FF/VI and UMEC/VI in Patients With COPD: Analysis of the Western Europe and North America Regions

Running header: COPD triple therapy in West Europe/North America

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Abbreviation list

COPD, chronic obstructive pulmonary disease; IMPACT, InforMing the Pathway of COPD Treatment; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol; FEV_1, forced expiratory volume in 1 second; SGRQ, St George's Respiratory Questionnaire; ITT, intent-to-treat; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; AE, adverse event; AESI, adverse events of special interest; SAE, serious adverse event.

Keywords: COPD, single-inhaler triple therapy, exacerbations, Western Europe, North America

Abstract

Background

The IMPACT trial demonstrated lower moderate/severe exacerbation rates with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI or UMEC/VI in patients with chronic obstructive pulmonary disease (COPD) and a history of exacerbations. Since IMPACT was a global study, post-hoc analyses were conducted by geographic region to investigate potential differences in overall findings.

Methods

IMPACT was a 52-week, randomized, double-blind trial. Patients with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year were randomized 2:2:1 to once-daily FF/UMEC/VI 100/62.5/25µg, FF/VI 100/25µg, or UMEC/VI 62.5/25µg. Endpoints assessed in the overall, Western Europe (WE) and North America (NA) populations included on-treatment moderate/severe exacerbation (rates and time-to-first), trough forced expiratory volume in 1 second and St George's Respiratory Questionnaire (SGRQ) total score. Safety was assessed.

Results

Overall, 10,355 patients were enrolled, 3164 from WE, 2639 from NA. FF/UMEC/VI significantly reduced on-treatment moderate/severe exacerbation rates versus FF/VI and UMEC/VI in WE (rate ratios 0.82 [95%CI 0.74-0.91], $P<.001$ and 0.76 [0.67-0.87], $P<.001$) and NA (0.87 [0.77-0.97], $P=.014$ and 0.69 [0.60-0.80], $P<.001$). FF/UMEC/VI reduced time-to-first moderate/severe exacerbation and improved lung function versus FF/VI and UMEC/VI in both regions, and improved SGRQ total score in WE, but not NA. Safety profiles were generally similar between

treatment groups/regions; the inhaled corticosteroid class effect of increased pneumonia incidence was seen in NA but not WE.

Conclusions

Consistent with intent-to-treat results, FF/UMEC/VI reduced moderate/severe exacerbation rate and risk and improved lung function in WE and NA; however, between-regions differences were seen for SGRQ total score and pneumonia incidence.

Clinical Trial Registration: NCT02164513.

Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by airflow limitation and progressive respiratory symptoms.[1] Global public health trends estimate that COPD burden will continue to rise, with COPD deaths estimated to increase to 4.4% of all deaths in Europe and 6.3% in the World Health Organization-defined region of the Americas by 2060.[2] There are differences in COPD burden in different regions reflecting variations in etiology,[3,4] disease severity,[5] symptoms,[6] medication use,[7] and healthcare systems and utilization.[7] These differences may help inform therapeutic strategies to optimize therapeutic approaches to reduce symptoms and exacerbation risk.[1]

In the global InforMing the Pathway of COPD Treatment (IMPACT) trial, single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) reduced moderate/severe exacerbation rates and improved lung function and health-related quality of life versus FF/VI or UMEC/VI dual therapy in patients ≥40 years of age with symptomatic COPD and a history of exacerbations.[8] Within trial populations, regional differences such as patient characteristics, treatment patterns, access to care and cultural/socioeconomic factors may dictate treatment choices and influence disease severity and progression in particular geographical locations. For example, a meta-analysis conducted in 2015 comprising 123 studies between 1990 and 2010 found that the overall prevalence of COPD as well as the rate of increase was higher in the Americas (including both North and South America) compared with Europe.[9] Furthermore, a cross sectional study assessing the burden of COPD symptoms in the USA and Europe found variations between patients across countries that had experienced at least one symptom of COPD.[10] In Europe, patients with more frequent symptoms were more likely to experience

worsening of symptoms and unexpected hospitalization. Whereas in the USA patients with

more frequent symptoms were not only more likely to experience worsening of symptoms but

also longer lasting symptoms and a longer length of exacerbations.[10] A further difference was

that treatment adherence was higher in the USA than Europe, however adherence was

consistent across patients in Europe when assessed by modified GOLD 2014 groups but varied

in the USA with adherence highest in GOLD Group C and lowest in Group A.[10] Therefore, it is

important to evaluate how overall population results pertain to patients treated in particular

regions. As IMPACT is one of the largest trials conducted in patients with COPD to date, we

have the unique opportunity to analyze study outcomes in patients enrolled in Western Europe

and North America, the two main regions from an enrollment perspective.

Materials and Methods

Study design and patients

IMPACT (GSK Study CTT116855; NCT02164513) was a 52-week, randomized, double-blind,

parallel-group, Phase III trial conducted in 37 countries.[8] The trial design has been previously

described.[8,11] Briefly, eligible patients with COPD were ≥40 years of age; symptomatic (COPD

Assessment Test [CAT] score ≥10); and had a forced expiratory volume in 1 second (FEV_1) <50%

predicted and ≥1 moderate/severe exacerbation in the preceding year, or FEV_1 50%–<80%

predicted and ≥2 moderate or ≥1 severe exacerbation in the preceding year. Patients were

randomized (2:2:1) to once-daily FF/UMEC/VI 100/62.5/25µg, FF/VI 100/25µg, or UMEC/VI

62.5/25µg administered via the ELLIPTA dry powder inhaler. Patients continued their existing

COPD medications during a 2-week run-in period and were provided with as-needed salbutamol

(rescue medication). All patients provided written informed consent. The trial was conducted in

accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval from local institutional review boards and independent ethics committees.

Endpoints, assessments, and data analysis

The primary endpoint was the annual rate of on-treatment moderate/severe exacerbations with FF/UMEC/VI versus FF/VI and UMEC/VI. Other efficacy endpoints included time-to-first moderate/severe exacerbation, change from baseline in trough FEV_1 and St George's Respiratory Questionnaire (SGRQ) total score at Week 52, and proportion of SGRQ responders (≥4 unit decrease from baseline in SGRQ total score) at Week 52. Treatment by region interaction for SGQR total score, moderate/severe exacerbation rate and trough FEV_1 was assessed. Moderate exacerbations were events requiring treatment with antibiotics and/or oral/systemic corticosteroids. Severe exacerbations were events resulting in hospitalization or death. The incidence of on-treatment adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI), and mortality was also assessed. In this post hoc analysis, outcomes were evaluated in the subgroups of patients enrolled in North America (USA, Puerto Rico, Canada) and Western Europe (pre-defined prior to unblinding as the European Economic Area and included Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Netherlands, Norway, Poland, Romania, Spain, Sweden, UK).Details of sample size calculations for the intent-to-treat (ITT) population have been described previously.[8,11] The trial was not powered for subgroup analysis by region. The ITT population included all randomized patients, except those randomized in error. The North America and Western Europe subgroups were derived from the ITT population. Statistical analyses are described in **e-Appendix 1**.

Results

Patients

Of 10,355 patients in the ITT population, 3164 (31%) were enrolled in Western Europe (1252 to FF/UMEC/VI, 1274 to FF/VI, 638 to UMEC/VI) and 2639 (25%) in North America (1072 to FF/UMEC/VI, 1046 to FF/VI, 522 to UMEC/VI). Baseline characteristics for each region (all treatments combined), are shown in **Table 1** and were similar between the three treatment groups within each population (**Supplementary Table 1**).

There were some between-region differences in baseline characteristics, notably a lower proportion of males in North America (50%) than Western Europe (64%) and the ITT population (66%), a higher mean number of smoking pack-years in North America (52.0) than the ITT population (46.6) and Western Europe (43.2), a higher baseline SGRQ total score in North America (54.8) than Western Europe (48.3) or the ITT population (50.2), and a lower proportion of patients experiencing ≥2 moderate or ≥1 severe exacerbation in the prior year in North America (66%) than Western Europe (71%) and the ITT population (70%). The proportion of patients on inhaled corticosteroids+long-acting β_2-agonist+long-acting muscarinic antagonist (ICS+LAMA+LABA) triple therapy at screening was higher in Western Europe (51%) than North America (46%) or the ITT population (40%), as was the proportion on LAMA+LABA at screening (19% vs 4% and 9%, respectively), while fewer patients were on ICS+LABA at screening in Western Europe (15%) than North America (31%) or the ITT population (32%). Most patients had blood eosinophil levels ≥100 cells/μL in all populations (**Figure 1**). A lower proportion of patients had blood eosinophil counts <100 cells/μL or <300 cells/μL in Western Europe (18% and 76%, respectively) than North America (28% and 82%, respectively) or the ITT population

(25% and 78%, respectively). Baseline blood eosinophil counts by country are given in **Supplementary Table 2** (mean), and **Supplementary Figure 1** and **Supplementary Figure 2** (distribution).

On-treatment moderate/severe exacerbations

In Western Europe, moderate/severe exacerbation rates were highest in the UK, followed by France and Denmark, and lowest in Romania and Poland (**Figure 2A**). In North America, rates were higher in Canada (**Figure 2B**). FF/UMEC/VI significantly reduced moderate/severe exacerbation rate and risk (time-to-first) versus either dual therapy in both regions, consistent with ITT results (**Figure 3** and **4**). Rate and risk reduction with FF/UMEC/VI versus FF/VI was numerically greater in Western Europe than North America or the ITT population, whereas for FF/UMEC/VI versus UMEC/VI it was numerically greater in North America than Western Europe or the ITT population (**Figure 3** and **4**). There was no significant interaction between treatment and region for this endpoint (**Supplementary Table 3**).

Trough FEV$_1$

Consistent with ITT results, FF/UMEC/VI significantly increased trough FEV$_1$ at Week 52 versus FF/VI in both regions, with numerically greater between-treatment increases in Western Europe than North America or the ITT population (**Figure 5**). FF/UMEC/VI significantly increased trough FEV$_1$ versus UMEC/VI in Western Europe and the ITT population. The point estimate favored FF/UMEC/VI over UMEC/VI in North America but was not statistically significant (**Figure 5**). Improvement in trough FEV$_1$ with FF/UMEC/VI versus UMEC/VI was numerically greater in Western Europe than North America, and similar between Western Europe and the ITT

population (**Figure 5**). There was no significant interaction between treatment and region for this endpoint (**Supplementary Table 3**).

SGRQ total score

All treatments improved SGRQ total score in both regions and in the ITT population, but statistically significant improvements were only demonstrated with FF/UMEC/VI versus FF/VI and UMEC/VI in Western Europe and the ITT population (**Figure 6A**). The magnitude of improvement from baseline in SGRQ total score with FF/UMEC/VI was greatest in the ITT population and smallest in Western Europe. Patients receiving either dual therapy regimen in Western Europe also experienced the smallest improvement in SGRQ total score compared with those in North America and the ITT population. However, between-treatment differences for FF/UMEC/VI versus both dual therapies were numerically greater in Western Europe than North America or the ITT population (**Figure 6A**). There was evidence of an overall treatment difference for SGRQ total score between regions (overall P = .054), which was mainly driven by the comparison between FF/UMEC/VI and FF/VI (P = .018) (**Supplementary Table 3**).

The proportion of SGRQ responders at Week 52 was significantly higher with FF/UMEC/VI than FF/VI or UMEC/VI in Western Europe and the ITT population. In North America, statistically significant differences were seen with FF/UMEC/VI versus UMEC/VI (P = .002) but not FF/VI (P = .081) (**Figure 6B**).

Safety

In both regions, the overall AE profile of FF/UMEC/VI was broadly similar to that of FF/VI and UMEC/VI. However, while pneumonia AESI incidence was higher in ICS-containing arms compared with UMEC/VI in North America and the ITT population, this was not seen in Western

Europe where incidences were similar across all treatment arms (**Table 2**). Incidence of SAEs and fatal SAEs of pneumonia was low (≤5% and <1%, respectively), with no difference between treatment groups and across regions.

Discussion

The IMPACT trial demonstrated the superiority of once-daily single-inhaler FF/UMEC/VI triple therapy over FF/VI or UMEC/VI dual therapy in reducing on-treatment moderate/severe exacerbation rates in a global population of patients with symptomatic COPD and a history of exacerbations.[8] Results from this geographical analysis in Western Europe and North America were broadly consistent with the benefits shown in the overall ITT population, and reductions in moderate/severe exacerbation rate and risk and improvements in lung function and health status were seen with FF/UMEC/VI compared with FF/VI or UMEC/VI. The safety profile of all treatments in both regions was generally in line with that in the ITT population. As expected based on the class effect for ICS,[12] the incidence of pneumonia was higher in ICS-containing arms compared with UMEC/VI in North America and the ITT population; interestingly this was not seen in Western Europe.

Studies have highlighted the burden of COPD in Western Europe and North America, revealing considerable variation across countries in patient characteristics, patterns of disease severity, symptoms, medication availability, access, and healthcare utilization.[10,13,14] These differences could impact the efficacy of COPD therapies in different populations. In this analysis, improvements in the rate and risk of moderate/severe exacerbations, trough FEV_1 and SGRQ responders with FF/UMEC/VI compared with UMEC/VI and FF/VI in both regions were generally

of a similar magnitude to those in the ITT population. FF/UMEC/VI significantly increased trough FEV_1 at Week 52 versus FF/VI in both regions; while a numerically greater between-treatment increase was seen in Western Europe compared with North America and the ITT population, this likely reflects the worsening of lung function in the FF/VI group in Western Europe rather than an increase in efficacy with FF/UMEC/VI. Statistically significant improvements in SGRQ total score were demonstrated with FF/UMEC/VI versus FF/VI and UMEC/VI in Western Europe and the ITT population but not in the North America region. The interaction term indicated an overall treatment difference between regions for this endpoint, mainly driven by the comparison between FF/UMEC/VI and FF/VI. Reasons for this are unknown but it is worth noting that baseline SGRQ total score was higher in the North American region compared with the Western Europe and ITT populations, indicating worse health status and greater changes from baseline were seen in all treatment groups in North America compared with Western Europe. The proportion of SGRQ responders at Week 52 was consistent across all regions for each treatment group; however, the difference between FF/UMEC/VI and FF/VI in the North America region was not statistically significant.

Baseline characteristics were similar across the two regions and the ITT population, with a few exceptions. The median blood eosinophil count in North America was lower than in Western Europe and the ITT population, and the mean number of smoking pack-years was higher. However, the percentage of patients with blood eosinophil counts <100 cell/μL was lower in Western Europe than in North America. Given the association between cigarette smoking and reduced ICS sensitivity,[15] along with improved ICS sensitivity in patients with higher eosinophil levels,[16] patients in North America may have been expected to have slightly lower sensitivity to

ICS-containing therapies based on their baseline characteristics. However, this was not reflected in the treatment effect of FF/UMEC/VI versus UMEC/VI and FF/VI on moderate/severe exacerbations. Differences in baseline treatment were noted according to region prior to randomization. The proportion of patients on LAMA+LABA therapy at screening was higher in Western Europe (19%) than North America (4%), while the proportion on ICS+LABA or ICS+LAMA+LABA at screening was higher in North America (77%) than Western Europe (66%). This may indicate different therapeutic requirements for patients enrolled in North America, which may explain why patients in this region appeared more responsive to FF than patients in Western Europe. Nevertheless, these differences in baseline treatment across regions did not appear to affect the treatment effect of FF/UMEC/VI versus either dual therapy.

There were large between-country variations in moderate/severe exacerbation rates, from 0.19 per patient-year in Romania to 2.10 per patient-year in the UK. These may be due to differences in patient demographics and clinical characteristics between countries, and highlight the potential difficulties in performing cross-trials comparisons unless correction for baseline demographics can be performed. When interpreting these between-country differences, it is worth noting that while the individual patient time at risk was broadly similar between countries, there was a large range of total duration at risk across countries, reflecting the varying sample sizes. As greater duration at risk would give more precision to the point estimates for annual rates of moderate/severe exacerbation, results in countries of small sample size need to be interpreted with caution.

Other studies have evaluated single-inhaler triple therapy versus dual or monotherapies;[17-20] however regional analyses have not been reported. The large sample size and global scope of the IMPACT trial allows for a robust comparison across different regions and the ITT population. Differences in national and international guidelines for COPD exist, including differences in treatment recommendations, potentially leading to regional differences in patient care.[1,21] It is important to understand these similarities and differences and how they may potentially affect patient management and inform future guideline development both globally and nationally. While the distribution and prevalence of COPD in different geographic regions has been well-studied,[22,23] a large-scale comparative assessment of how treatment efficacy can vary by region has not been previously described. Results in these two IMPACT regional subpopulations were consistent with the overall study population and demonstrate the favorable benefit-risk profile of single-inhaler FF/UMEC/VI triple therapy over FF/VI or UMEC/VI dual therapy in patients with symptomatic COPD and a history of exacerbations. However, it should be noted that these analyses are descriptive and were conducted post hoc, and the study was not powered to demonstrate statistical significance for any endpoints by or between regions.

Conclusions

In this regional analysis of the IMPACT trial, FF/UMEC/VI significantly reduced the rate and risk of moderate/severe exacerbations versus FF/VI and UMEC/VI in both the Western Europe and North America regions. Treatment responses were similar with respect to exacerbations and lung function for both regions and the ITT population. However, there were some differences in SGRQ total score between regions, with no differential effect observed between FF/UMEC/VI and dual therapies in North America, unlike in Western Europe and the ITT population. Safety

profiles with FF/UMEC/VI, UMEC/VI and FF/VI were similar in both regions and the ITT

population although the ICS class effect of increased pneumonia incidence was seen in North

America and the ITT population, but not in Western Europe. These efficacy and safety results in

patients with symptomatic COPD and a history of exacerbations continue to support a positive

benefit-risk profile with FF/UMEC/VI.

Disclosures:

Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. A Bourdin, G Criner, G Devouassoux, M Dransfield, DMG Halpin, JM Echave-Sustaeta María-Tomé, NA Hanania, R Kalhan, and TM Siler contributed to the acquisition of data and data analysis and interpretation. MK Han, CE Jones, P Lange, S Lettis, DA Lomas, N Martin, FJ Martinez, H Quasny, L Sail, D Singh, B Thomashow, H Watz and R Wise contributed to data analysis and interpretation. DA Lipson contributed to study conception and design, and data analysis and interpretation.

Conflict of interests:

A Bourdin was an investigator in the IMPACT trial and has received personal fees and a grant from Boehringer Ingelheim, personal fees from AstraZeneca, Chiesi, GSK, Novartis and Sanofi-Regeneron, and is an investigator in clinical trials from Nuvaira, Pulmonx, Actelion, MSD, United Therapeutic, Vertex, Acceleron, and Galapagos.

G Criner has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSA Medical, Eolo, GSK, HGE Technologies, Novartis, Nuvaira, Olympus, Pulmonx, and Verona.

DA Lomas reports personal fees from GSK and Grifols; he chaired the GSK Respiratory Therapy Area Board in 2012–2015.

JM Echave-Sustaeta María-Tomé has received personal fees from GSK and was an investigator in the IMPACT trial.

FJ Martinez has received personal fees and non-financial support from, AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Inova Fairfax Health System, Miller Communications, National Society for Continuing Education, Novartis, Pearl Pharmaceuticals, PeerView Communications, Prime Communications, Puerto Rico Respiratory Society, Chiesi, Sunovion, Theravance, Potomac, University of Alabama Birmingham, Physicians Education Resource, Canadian Respiratory Network, Teva and Dartmouth; and personal fees from Columbia University, MD Magazine, Methodist Hospital Brooklyn, New York University, UpToDate, WebMD/MedScape, Patara/Respivant, American Thoracic Society, Rockpointe, Rare Disease Healthcare Communications and France Foundation, and has taken part in advisory boards for AstraZeneca, Boehringer Ingelheim, ProterrixBio, Genentech, Novartis, Pearl Pharmaceuticals, Theravance, Zambon, Gala, Chiesi, GSK, Sunovion, and Teva, steering committees for AstraZeneca, Pearl Pharmaceuticals, Afferent/Merck, Gilead, Nitto, Patara/Respivant, Biogen, Veracyte, Prometic, Bayer, ProMedior and GSK, and been an advisor for Bridge Biotherapeutics.

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Other contributions

Data availability

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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Tables

Table 1: Baseline characteristics (ITT populations)

	Western Europe (N = 3164)	North America (N = 2639)	ITT (N = 10,355)
Age, mean (SD), years	64.2 (8.0)	65.1 (8.5)	65.3 (8.3)
Male, n (%)	2014 (64)	1330 (50)	6870 (66)
Ethnicity, n (%)			
Not Hispanic/Latino	3108 (98)	2564 (97)	8693 (84)
Hispanic/Latino	55 (2)	75 (3)	1661 (16)
BMI, mean (SD), kg/m^2	27.1 (5.7)	28.4 (6.8)	26.6 (6.1)
Smoking status, n (%)			
Former smoker	1895 (60)	1611 (61)	6768 (65)
Current smoker	1269 (40)	1028 (39)	3587 (35)
Smoking history (pack-years), mean (SD)	43.2 (22.7)	52.0 (28.3)	46.6 (26.6)
SGRQ total score, mean (SD)	48.3 (15.8)	54.8 (15.2)	50.7 (16.9)
Post-bronchodilator FEV$_1$, L, mean (SD)	1.345 (0.482)	1.225 (0.491)	1.272 (0.486)
Post-bronchodilator FEV$_1$ % predicted, mean (SD)	46.0 (14.0)	44.3 (14.9)	45.5 (14.8)
Post-bronchodilator FVC, L, mean (SD)	2.805 (0.835)	2.589 (0.832)	2.726 (0.819)
Post-bronchodilator FEV$_1$/FVC ratio, mean (SD)	0.484 (0.115)	0.476 (0.118)	0.470 (0.120)
Exacerbation history in prior 12 months, n (%)			
1 moderate and 0 severe	932 (29)	887 (34)	3056 (30)

≥2 moderate or ≥1 severe	2232 (71)	1752 (66)	7299 (70)
Blood eosinophil count (cells/µL), median (IQR)	180 (110–280)	150 (90–250)	170 (90–270)
COPD medication at screening*, n (%)			
ICS+LAMA+LABA	1612 (51)	1217 (46)	4183 (40)
LAMA+LABA	589 (19)	100 (4)	934 (9)
ICS+LABA	467 (15)	818 (31)	3341 (32)
LAMA	271 (9)	226 (9)	831 (8)

*Between day of screening -3 days and date of screening (inclusive). BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; IQR = interquartile range; ITT = intent-to-treat; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SD = standard deviation.

Table 2: Incidence of on-treatment AEs (ITT populations)

AE incidence, n (%)	Western Europe			North America			ITT		
	FF/UMEC/VI n = 1252	FF/VI n = 1274	UMEC/VI n = 638	FF/UMEC/VI n = 1071	FF/VI n = 1046	UMEC/VI n = 522	FF/UMEC/VI n = 4151	FF/VI n = 4134	UMEC/VI n = 2070
Any on-treatment AE	880 (70)	845 (66)	436 (68)	790 (74)	739 (71)	360 (69)	2897 (70)	2800 (68)	1429 (69)
Leading to permanent study treatment discontinuation/study withdrawal	87 (7)	114 (9)	58 (9)	75 (7)	98 (9)	57 (11)	252 (6)	327 (8)	187 (9)
On-treatment AESI									
Anticholinergic syndrome (SMQ)	49 (4)	43 (3)	28 (4)	67 (6)	43 (4)	15 (3)	184 (4)	140 (3)	70 (3)
Asthma/bronchospasm (SMQ)	6 (<1)	2 (<1)	1 (<1)	15 (1)	19 (2)	6 (1)	27 (<1)	34 (<1)	16 (<1)
Cardiovascular effects	125 (10)	116 (9)	63 (10)	147 (14)	135 (13)	59 (11)	450 (11)	430 (10)	224 (11)
Decreased BMD and associated fractures	24 (2)	25 (2)	14 (2)	41 (4)	25 (2)	13 (2)	98 (2)	85 (2)	37 (2)

Effects on potassium	4 (<1)	2 (<1)	3 (<1)	19 (2)	12 (1)	3 (<1)	34 (<1)	25 (<1)	8 (<1)
Gastrointestinal obstruction (SMQ)	2 (<1)	3 (<1)	0 (0)	5 (<1)	4 (<1)	0 (0)	9 (<1)	10 (<1)	2 (<1)
Hyperglycemia/new onset DM (SMQ)	43 (3)	29 (2)	29 (5)	50 (5)	48 (5)	24 (5)	152 (4)	117 (3)	73 (4)
Hypersensitivity	54 (4)	45 (4)	26 (4)	66 (6)	57 (5)	31 (6)	196 (5)	195 (5)	95 (5)
LRTI excluding pneumonia	39 (3)	42 (3)	13 (2)	42 (4)	36 (3)	29 (6)	200 (5)	199 (5)	108 (5)
Local steroid effects	109 (9)	100 (8)	35 (5)	119 (11)	93 (9)	36 (7)	337 (8)	301 (7)	108 (5)
Ocular effects	21 (2)	16 (1)	6 (<1)	19 (2)	10 (<1)	5 (<1)	55 (1)	45 (1)	26 (1)
Pneumonia	70 (6)	54 (4)	30 (5)	99 (9)	86 (8)	20 (4)	317 (8)	292 (7)	97 (5)
Tremor	6 (<1)	2 (<1)	2 (<1)	1 (<1)	0 (0)	2 (<1)	8 (<1)	4 (<1)	6 (<1)
Urinary retention	0 (0)	3 (<1)	4 (<1)	6 (<1)	7 (<1)	2 (<1)	8 (<1)	12 (<1)	9 (<1)
Any on-treatment SAE	272 (22)	262 (21)	149 (23)	264 (25)	228 (22)	124 (24)	895 (22)	850 (21)	470 (23)
Any on-treatment fatal SAE	19 (2)	17 (1)	11 (2)	18 (2)	15 (1)	13 (2)	68 (2)	76 (2)	49 (2)

AE = adverse event; AESI = adverse event of special interest (AEs which have specified areas of interest for FF, UMEC, or VI, or for patients with COPD); BMD = bone mineral

density; DM = diabetes mellitus; FF = fluticasone furoate; LRTI = lower respiratory tract infection; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients

in subgroup; SAE =serious adverse event; SMQ = Standardized MedDRA Query; UMEC = umeclidinium; VI = vilanterol.

Figure legends

Figure 1: Baseline blood eosinophil counts (ITT populations)
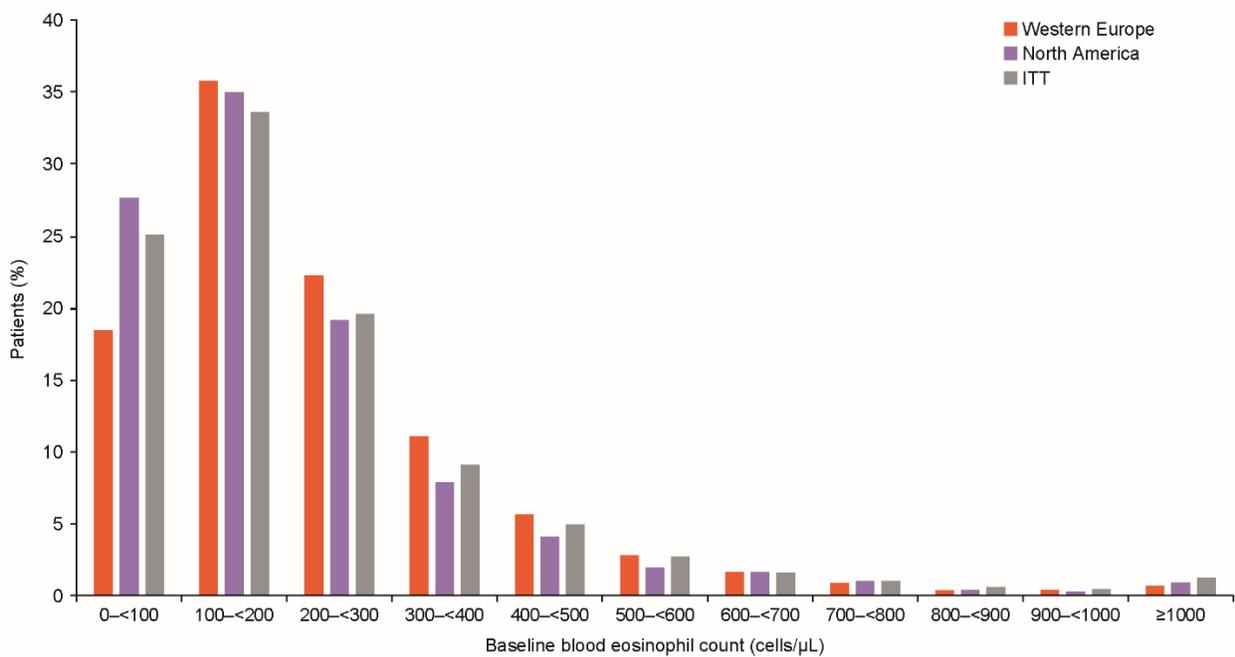
ITT, intent-to-treat.

Figure 2: Rate of on-treatment moderate/severe exacerbations per patient-year by country in

Western Europe and North America (all treatments combined)

	Annual rate	Number of patients	Duration at risk	Patients with moderate/severe exacerbation, n (%)
Western Europe				
Austria	1.01	119	102.9	59 (50)
Belgium	1.25	109	104.5	58 (53)
Czech Republic	0.77	143	134.0	60 (42)
Denmark	1.75	90	66.4	65 (72)
Finland	1.57	76	63.2	48 (63)
France	1.75	134	111.5	87 (65)
Germany	0.83	1187	996.8	513 (43)
Netherlands	1.36	301	238.2	197 (65)
Norway	1.60	76	51.3	40 (53)
Poland	0.45	88	80.8	29 (33)
Romania	0.19	103	98.9	17 (17)
Spain	1.41	499	443.3	316 (63)
Sweden	1.57	92	65.0	63 (68)
United Kingdom	2.10	147	113.0	110 (75)
North America				
Canada	1.55	212	171.3	132 (62)
Puerto Rico	0.45	21	15.5	4 (19)
United States	1.19	2406	1927.7	1298 (54)

Annual rate of moderate/severe exacerbations (events per patient-year)

Figure 3: Rate of on-treatment moderate/severe exacerbations
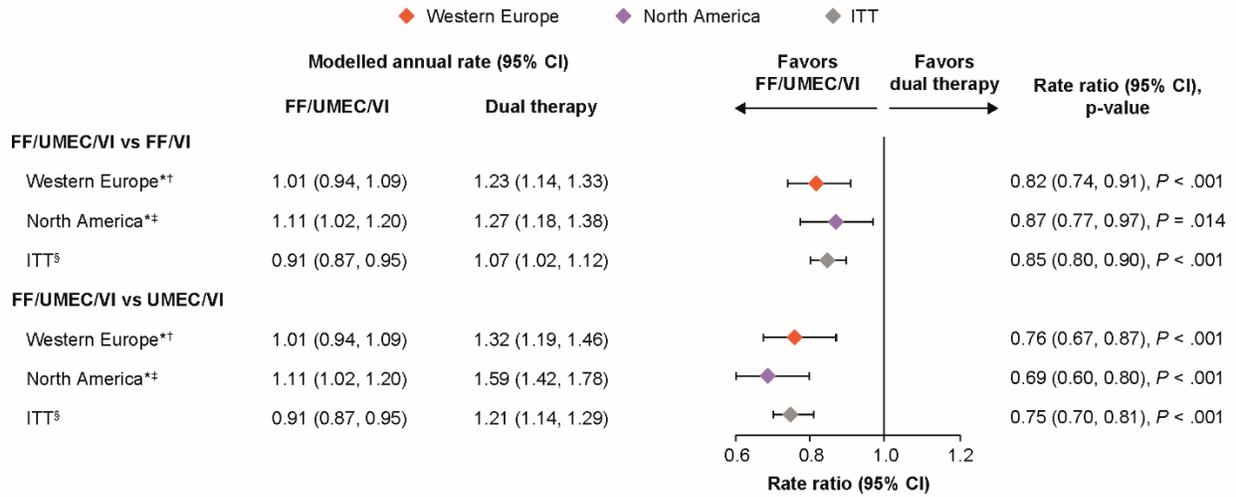
*Post hoc analysis; †N = 3164 (FF/UMEC/VI, n = 1252; FF/VI, n = 1274; UMEC/VI, n = 638); ‡N = 2639 (FF/UMEC/VI, n = 1072;

FF/VI, n = 1046; UMEC/VI, n = 522); §N = 10,355 (FF/UMEC/VI, n = 4151; FF/VI, n = 4134; UMEC/VI, n = 2070). CI = confidence

interval; FF = fluticasone furoate; ITT = intent-to-treat; UMEC = umeclidinium; VI = vilanterol.

## *Figure 4: Risk (TTF) of on-treatment moderate/severe exacerbations*

	Patients with an event, n/N (%)		Favors FF/UMEC/VI ← → Favors dual therapy	Hazard ratio (95% CI), p-value
	FF/UMEC/VI	Dual therapy		
FF/UMEC/VI vs FF/VI				
Western Europe*	632/1252 (50)	686/1274 (54)		0.81 (0.73, 0.90), *P* < .001
North America*	573/1071 (54)	561/1046 (54)		0.87 (0.77, 0.98), *P* = .018
ITT	1959/4151 (47)	2039/4134 (49)		0.85 (0.80, 0.91), *P* < .001
FF/UMEC/VI vs UMEC/VI				
Western Europe*	632/1252 (50)	344/638 (54)		0.83 (0.73, 0.95), *P* = .005
North America*	573/1071 (54)	300/522 (57)		0.78 (0.68, 0.89), *P* < .001
ITT	1959/4151 (47)	1036/2070 (50)		0.84 (0.78, 0.91), *P* < .001

*Post hoc analysis. CI = confidence interval; FF = fluticasone furoate; ITT = intent-to-treat; n = number of patients with an event;

N = number of patients in subgroup; TTF = time-to-first; UMEC = umeclidinium; VI = vilanterol.

Figure 5: Change from baseline in trough FEV$_1$ (mL) at Week 52
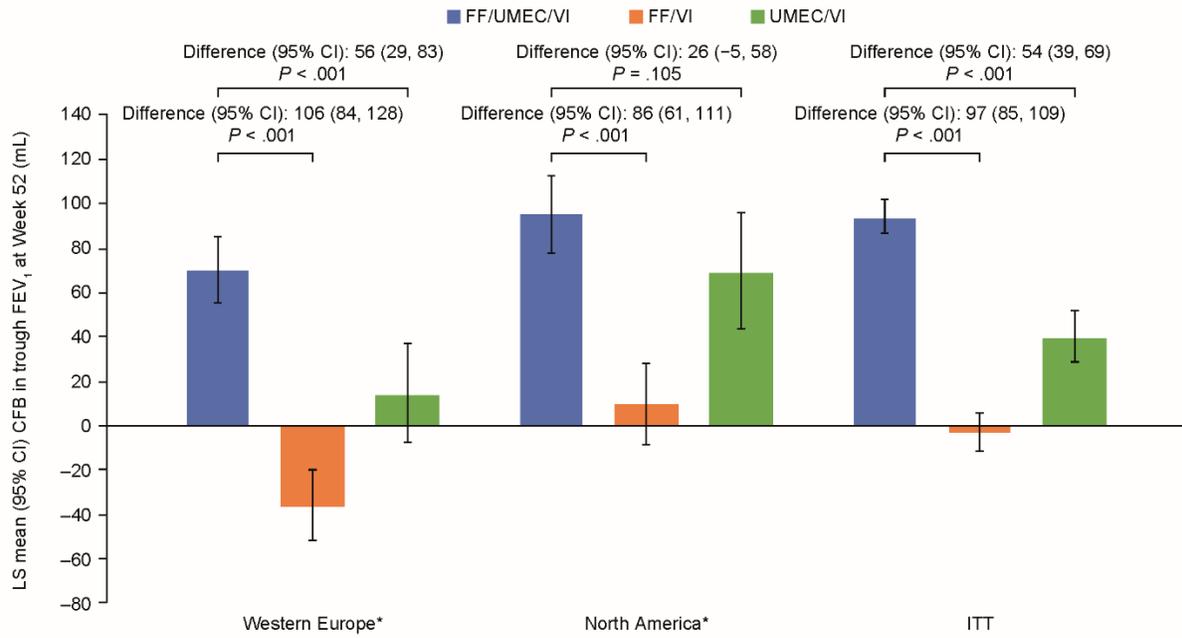
*Post hoc analysis. CFB = change from baseline; CI = confidence interval; FEV$_1$ = forced expiratory volume in 1 second;

FF = fluticasone furoate; ITT = intent-to-treat; LS = least squares; UMEC = umeclidinium; VI = vilanterol.

Figure 6: (A) Change from baseline in SGRQ total score and (B) SGRQ responders at Week 52
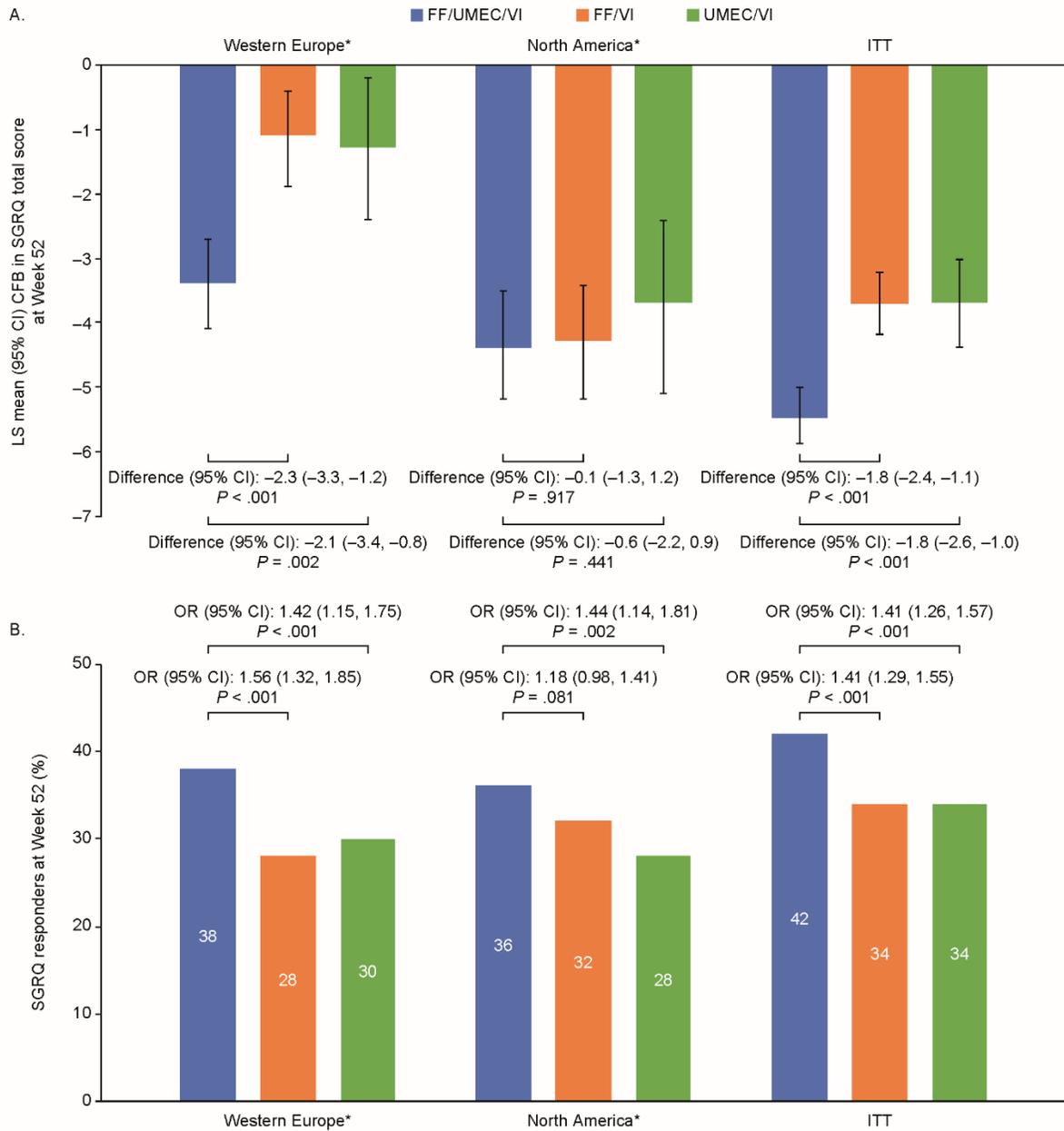
*Post hoc analysis. SGRQ responders are patients with a ≥4-unit decrease from baseline in SGRQ total score. CFB = change from baseline; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; FF = fluticasone furoate; ITT = intent-to-treat; LS = least squares; OR = odds ratio; UMEC = umeclidinium; VI = vilanterol.