The IMPACT Trial: Single Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: Results on Cardiovascular Safety

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Introduction

- In the InforMing the PAthway of COPD Treatment (IMPACT) trial, once-daily single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) reduced the rate of moderate/severe exacerbations and improved lung function and health-related quality of life compared with dual therapy with FF/VI or UMEC/VI in patients ≥40 years of age with symptomatic chronic obstructive pulmonary disease (COPD) and a history of exacerbations.[1]
- Cardiovascular (CV) disease, for example, coronary artery disease, heart failure and arrythmias, is a common comorbidity of COPD and an exacerbation in COPD symptoms is associated with elevated CV disease risk or worse outcomes in patients with COPD and CV disease.[2,3]
- While studies have suggested that the use of bronchodilators is associated with increased CV risk in patients with COPD, a recent systematic review concluded that, although no specific CV safety signals have emerged, more data are needed in patients with high CV risk.[3]
- In the IMPACT trial, patients with significant concurrent CV disease/risk were included. This allows the assessment of CV safety of inhaled COPD therapy in a population more representative of real-world clinical practice. The aim of these analyses was to assess safety in patients with CV disease/risk in the intent-to-treat (ITT) population of the IMPACT trial.

Methods

- IMPACT (GSK Study CTT116855; NCT02164513; N=10,355) was a 52-week randomized, double-blind, multicenter Phase III study, which compared the efficacy and safety of once-daily single-inhaler triple therapy with FF/UMEC/VI 100/62.5/25 mcg with once-daily dual therapy with FF/VI 100/25 mcg or UMEC/VI 62.5/25 mcg in patients ≥40 years of age with symptomatic COPD (COPD Assessment Test score ≥10) and ≥1 moderate/severe exacerbation in the previous year.[1]
- Patients with a past history of previous myocardial infarction (MI) (>6 months prior to Screening), New York Heart Association Class 1–3 heart failure, and unstable or life-threatening cardiac arrhythmia requiring intervention (>3 months prior to Screening) were eligible to participate in the study.
- On-treatment CV safety and the incidence of major adverse cardiac events (MACE) were assessed as pre-specified analyses in the IMPACT trial.
- On-treatment safety assessments included: incidence of CV adverse events (AEs) of special interest (CVAESIs); time-to-first (TTF) CVAESI, and TTF serious CVAESI resulting in hospitalization/prolonged hospitalization or death; and incidence and rate of MACE. CVAESIs were prespecified AEs associated with the use of inhaled corticosteroid, long-acting muscarinic antagonist and long-acting β_2-agonist. CVAESIs included: cardiac arrhythmia, cardiac failure, ischemic heart disease, hypertension, and central nervous system (CNS) hemorrhages and cerebrovascular conditions (including ischemic stroke). Serious AEs (SAEs) were assessed by an independent adjudication committee that categorized the primary event in the SAE report.
- MACE was determined from the adjudicated CV deaths and investigator-reported non-fatal AEs, and was broadly and narrowly defined. Broad MACE included adjudicated CV deaths, non-fatal CNS hemorrhages and cerebrovascular conditions Standardized MedDRA Query (SMQ), non-fatal MI SMQ, and non-fatal other ischemic heart disease SMQ. Narrow MACE included adjudicated CV deaths, nonfatal CNS hemorrhages and cerebrovascular conditions SMQ, and non-fatal MI and acute MI Preferred Terms.
- MACE incidence was reported as a percentage and exposure-adjusted rate per 1000-patient years.
- TTF analyses of CVAESIs were conducted using a Cox proportional hazards model with covariates of treatment group and geographical region.

Results

Patients

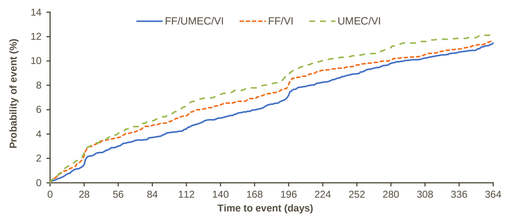
- Baseline characteristics, CV disorders and risk factors by treatment group for the ITT population are summarized in **Table 1**.
- At baseline, 16% (n=1620) of patients reported a current cardiac disorder (coronary artery disease n=952 [9%]; arrhythmia n=482 [5%]; congestive heart failure n=389 [4%]; angina pectoris n=342 [3%], MI n=1 [<1%]). Overall, 68% of patients (n=7012) had ≥1 CV risk factor and 40% (n=4127) had ≥2. Reported frequency of risk factors was consistent across treatment groups. The CV risk factors most frequently reported (≥10%) were hypertension (53%), hypercholesterolemia (33%), diabetes mellitus (15%), and coronary artery disease (12%; **Table 1**).

Table 1. Baseline characteristics, CV disorders, and risk factors (ITT population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070	Overall N=10,355
Age, mean (SD), years	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
Gender, male, n (%)	2766 (67)	2748 (66)	1356 (66)	6870 (66)
BMI, mean (SD), kg/m²	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)	26.6 (6.1)
Smoking status, n (%)				
Current smoker	1436 (35)	1423 (34)	728 (35)	3587 (35)
Former smoker	2715 (65)	2711 (66)	1342 (65)	6768 (65)
CV risk factors, n (%)				
0	1365 (33)	1322 (32)	656 (32)	3343 (32)
1	1147 (28)	1158 (28)	580 (28)	2885 (28)
≥2	1639 (39)	1654 (40)	834 (40)	4127 (40)
Cardiac disorders, n (%)	656 (16)	636 (15)	328 (16)	1620 (16)
Vascular disorders, n (%)	2087 (50)	2170 (52)	1086 (52)	5343 (52)
CV risk factors, n (%)				
Hypertension	2132 (51)	2207 (53)	1107 (53)	5446 (53)
Hypercholesterolemia	1354 (33)	1332 (32)	681 (33)	3367 (33)
Diabetes mellitus	641 (15)	645 (16)	313 (15)	1599 (15)
Coronary artery disease	510 (12)	488 (12)	254 (12)	1252 (12)
Arrhythmia	335 (8)	323 (8)	158 (8)	816 (8)
Angina pectoris	291 (7)	307 (7)	139 (7)	737 (7)
MI	270 (7)	274 (7)	137 (7)	681 (7)
Congestive heart failure	223 (5)	192 (5)	124 (6)	539 (5)
Cerebrovascular accident	199 (5)	165 (4)	94 (5)	458 (4)
Vascular disease*	133 (3)	148 (4)	61 (3)	342 (3)

*Carotid or aorto-femoral. BMI, body mass index; SD, standard deviation

Figure 1. Kaplan–Meier plot of TTF on-treatment CVAESI



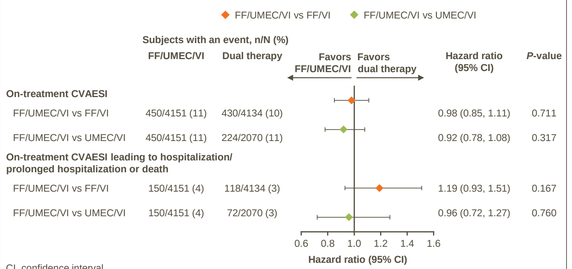
Number of patients at risk

FF/UMEC/VI	4151	4019	3849	3758	3674	3570	3511	3446	3339	3288	3228	3170	3134	2352
FF/VI	4134	3883	3652	3526	3426	3294	3228	3156	3037	2994	2956	2907	2870	2156
UMEC/VI	2070	1935	1812	1741	1684	1615	1579	1542	1484	1462	1436	1403	1388	1051

TTF CVAESI

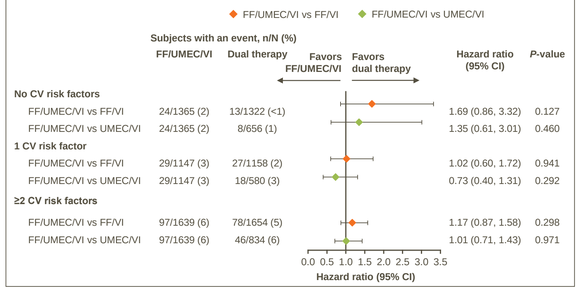
- Incidence of on-treatment CVAESI was 11% for both FF/UMEC/VI and UMEC/VI, and 10% for FF/VI.
  - There was no statistical difference in TTF CVAESI for FF/UMEC/VI versus FF/VI or UMEC/VI (**Figure 1** and **2**).
- Incidence of CVAESI leading to hospitalization/prolonged hospitalization or death was 4%, 3%, and 3% for FF/UMEC/VI, FF/VI, and UMEC/VI, respectively.
  - There was no statistical difference in TTF CVAESI leading to hospitalization/prolonged hospitalization or death for FF/UMEC/VI versus FF/VI or UMEC/VI in the overall study population (**Figure 2**) or any CV risk factor subgroup (**Figure 3**).

Figure 2. TTF on-treatment CVAESI and CVAESI leading to hospitalization/prolonged hospitalization or death



CI, confidence interval

Figure 3. TTF on-treatment CVAESI leading to hospitalization/prolonged hospitalization or death in ≥3% of any treatment group according to CV risk factors



Incidence of MACE

- The incidence and exposure-adjusted rates for any on-treatment MACE events using the broad and narrow definitions were similar across treatment groups, with no consistent pattern between individual MACE categories (**Table 2**).
- Narrow MACE incidence (exposure-adjusted rate) was 2% (22.3 per 1000 patient-years) for FF/UMEC/VI, 1% (18.8 per 1000 patient-years) for FF/VI, and 2% (22.4 per 1000 patient-years) for UMEC/VI.
- Broad MACE incidence (exposure-adjusted rate) was 3% (44.7 per 1000 patient-years) for FF/UMEC/VI, 2% (35.3 per 1000 patient-years) for FF/VI, and 3% (44.8 per 1000 patient-years) for UMEC/VI.

Table 2. Incidence of MACE

	FF/UMEC/VI (N=4151)		FF/VI (N=4134)		UMEC/VI (N=2070)	
	Patients with MACE n (%)	MACE events n (rate)*	Patients with MACE n (%)	MACE events n (rate)*	Patients with MACE n (%)	MACE events n (rate)*
Narrow definition						
Any MACE	80 (2)	83 (22.3)	60 (1)	65 (18.8)	37 (2)	38 (22.4)
Adjudicated CV death	20 (<1)	20 (5.4)	27 (<1)	27 (7.8)	16 (<1)	16 (9.4)
Non-fatal CNS hemorrhages and cerebrovascular conditions (SMQ)	38 (<1)	40 (10.8)	21 (<1)	25 (7.2)	10 (<1)	10 (5.9)
Non-fatal MI (PT)	9 (<1)	9 (2.4)	6 (<1)	6 (1.7)	5 (<1)	5 (2.9)
Non-fatal acute MI (PT)	13 (<1)	14 (3.8)	7 (<1)	7 (2.0)	7 (<1)	7 (4.1)
Broad definition						
Any MACE	133 (3)	166 (44.7)	100 (2)	122 (35.3)	66 (3)	76 (44.8)
Adjudicated CV death	20 (<1)	20 (5.4)	27 (<1)	27 (7.8)	16 (<1)	16 (9.4)
Non-fatal CNS hemorrhages and cerebrovascular conditions (SMQ)	38 (<1)	40 (10.8)	21 (<1)	25 (7.2)	10 (<1)	10 (5.9)
Non-fatal MI (SMQ)	49 (1)	52 (14.0)	29 (<1)	32 (9.3)	24 (1)	25 (14.7)
Non-fatal other ischemic heart disease (SMQ)	41 (<1)	54 (14.5)	32 (<1)	38 (11.0)	25 (1)	25 (14.7)

*Rate was event rate per 1000 patient-years, calculated as the number of events x 1000, divided by the total treatment exposure. PT, Preferred Term

Conclusions

- In a symptomatic COPD population with a history of exacerbations and a high rate of CV disease/risk, the incidence and risk of CVAESI and MACE events were low and similar across treatment arms.
- These results for FF/UMEC/VI are consistent with a network meta-analysis, which demonstrated that no additive CV risk was associated with bronchodilator combinations,[4] and the extensive CV safety database from FF/VI, UMEC/VI, and UMEC.

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Disclosures

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