The IMPACT Trial: Single Inhaler Triple Therapy Fluticasone Furoate/Umeclidinium/Vilanterol Versus Fluticasone Furoate/Vilanterol and Umeclidinium/Vilanterol in Patients With COPD: A Pre-Specified Analysis of Safety According to Age

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Introduction

- Chronic obstructive pulmonary disease (COPD) is primarily a disease of older adults, and its prevalence increases with age.[1,2]
- While inhaled medications are a mainstay of COPD treatment,[3] age-related differences in pharmacokinetic or pharmacodynamic profiles may lead to differences in safety profiles between older and younger individuals, further compounded by concomitant comorbidities and the potential for polypharmacy in older patients.[4,5]
- The InforMing the PAthway of COPD Treatment (IMPACT) trial showed that single-inhaler triple therapy containing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) results in a lower rate of moderate/severe exacerbations versus dual therapy with FF/VI or UMEC/VI, with a similar safety profile, in patients with symptomatic COPD and a history of exacerbations.[6] On-treatment, pre-specified safety assessments of IMPACT trial data were evaluated by age.

Methods

- IMPACT (GSK study CTT116855; NCT02164513) was a Phase III, double-blind, parallel-group, 52-week, multicenter study in patients ≥40 years of age with symptomatic COPD and ≥1 moderate/severe exacerbation in the prior year (N=10,355). Patients were randomized 2:2:1 to FF/UMEC/VI 100/62.5/25 mcg (N=4151), FF/VI 100/25 mcg (N=4134), or UMEC/VI 62.5/25 mcg (N=2070), all administered once daily via the ELLIPTA inhaler.[6]
- On-treatment safety assessments in the intent-to-treat (ITT) population included adverse events (AEs), serious AEs (SAEs), AEs leading to permanent discontinuation of study treatment or withdrawal from the study, and AEs of special interest (AESIs; AEs which have specified areas of interest for inhaled corticosteroids, long-acting muscarinic receptor antagonists, or long-acting β_2-agonists, or for patients with COPD).
- The safety assessments for the ITT population have been published elsewhere.[6] This analysis examined the safety profile of each treatment arm (FF/UMEC/VI, FF/VI, and UMEC/VI) by age.
- Pre-specified summaries were conducted according to the following age categories: ≤64, 65–74, and 75–84 years of age. The age group ≥85 years is not included here due to the small proportion of subjects in each treatment group (all <1%). Safety assessments are presented descriptively.

Results

Patients

- The ITT population comprised 10,355 patients, of which 46% (n=4724) were ≤64 years old, 41% (n=4225) were 65–74 years old, 13% (n=1328) were 75–84 years old, and <1% (n=78) were ≥85 years old.
- Baseline characteristics for the ≤64, 65–74, and 75–84 years subgroups are summarized in **Table 1**. In each age group, no differences in baseline characteristics were identified across the 3 treatment groups.
  - The 75–84 years subgroup had the highest proportion of patients with ≥2 moderate/severe exacerbations in the prior year, ≥2 cardiovascular (CV) risk factors or a past history of pneumonia.

Table 1. Baseline characteristics by age group

	Age ≤64 years (N=4724)	Age 65–74 years (N=4225)	Age 75–84 years (N=1328)
Age (years), mean (SD)	58.0 (4.8)	69.1 (2.8)	77.8 (2.4)
Gender (male), n (%)	2853 (60)	2949 (70)	1004 (76)
Current smoker, n (%)	2254 (48)	1143 (27)	186 (14)
Former smoker, n (%)	2470 (52)	3082 (73)	1142 (86)
BMI (kg/m²), mean (SD)	27.0 (6.6)	26.5 (5.8)	25.7 (5.2)
Moderate/severe exacerbation history in prior year, n (%)*			
<2	2175 (46)	1930 (46)	568 (43)
≥2	2549 (54)	2295 (54)	760 (57)
CV risk factors, n (%)†			
0	1954 (41)	1105 (26)	269 (20)
1	1316 (28)	1203 (28)	346 (26)
≥2	1454 (31)	1917 (45)	713 (54)
Past history of pneumonia, n (%)‡			
Yes	968 (21)	1012 (24)	343 (26)
No	3749 (79)	3207 (76)	985 (74)

*Moderate exacerbations were those requiring treatment with antibiotics and/or oral/systemic corticosteroids. Severe exacerbations were those resulting in hospitalization or death; †CV risk factors included current or past history of angina pectoris, coronary artery disease, myocardial infarction, arrhythmia, congestive heart failure, hypertension, cerebrovascular accident, carotid or aorto-femoral vascular disease, diabetes mellitus and hypercholesterolemia; ‡age ≤64 years: n=4717; age 65–74 years: n=4219; age 75–84: n=1328.
BMI, body mass index; SD, standard deviation

Safety

- The incidence of on-treatment AEs was similar across all three treatment groups for patients ≤64, 65–74, and 75–84 years of age. The incidence of on-treatment AEs was highest in patients 75–84 years of age in the FF/UMEC/VI and UMEC/VI groups (**Figure 1**).
- The incidence of on-treatment SAEs was similar across the three treatment groups for patients ≤64, 65–74, and 75–84 years of age. The incidence of on-treatment SAE was higher in those 75–84 years of age in the FF/UMEC/VI and FF/VI groups, and in patients 65–74 years of age in the UMEC/VI group, although numbers were low (**Figure 2**).
- The incidence of AEs leading to permanent discontinuation of study treatment or withdrawal from the study was similar for all three treatment groups for subjects ≤64, 65–74, and 75–84 years of age, although numbers were low (**Figure 3**).

Figure 1. Incidence of on-treatment AEs (ITT population and age subgroups)

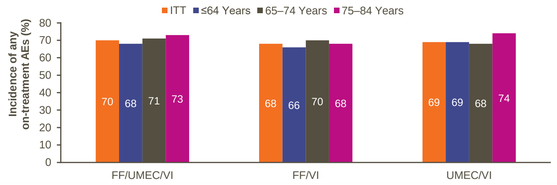

Figure 2. Incidence of on-treatment SAEs (ITT population and age subgroups)

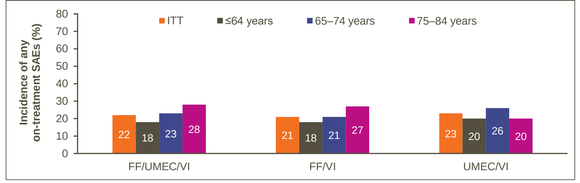

Figure 3. Incidence of AEs leading to treatment discontinuation or study withdrawal (ITT population and age subgroups)

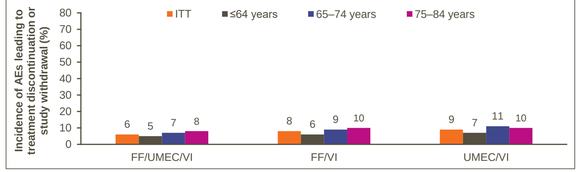

Table 2. Incidence of on-treatment AESIs by age group

	FF/UMEC/VI			FF/VI			UMEC/VI		
Age group, years	**≤64 (n=1886)**	**65–74 (n=1700)**	**75–84 (n=530)**	**≤64 (n=1876)**	**65–74 (n=1693)**	**75–84 (n=537)**	**≤64 (n=962)**	**65–74 (n=832)**	**75–84 (n=261)**
Duration at risk, patient-years	1689.1	1530.9	465.8	1604.4	1401.8	428.1	817.9	661.8	208.5
n (%)									
Anticholinergic syndrome (SMQ)	68 (4)	83 (5)	30 (6)	64 (3)	56 (3)	18 (3)	30 (3)	32 (4)	7 (3)
Asthma/bronchospasm (SMQ)	16 (<1)	9 (<1)	2 (<1)	19 (1)	11 (<1)	4 (<1)	7 (<1)	5 (<1)	3 (1)
CV effects	171 (9)	186 (11)	84 (16)	176 (9)	176 (10)	71 (13)	99 (10)	91 (11)	31 (12)
Decreased BMD and associated fractures	49 (3)	35 (2)	13 (2)	29 (2)	33 (2)	21 (4)	18 (2)	14 (2)	5 (2)
Effects on potassium	17 (<1)	14 (<1)	3 (<1)	7 (<1)	14 (<1)	4 (<1)	4 (<1)	4 (<1)	0 (0)
Gastrointestinal obstruction (SMQ)	1 (<1)	6 (<1)	2 (<1)	6 (<1)	3 (<1)	0 (0)	0 (0)	2 (<1)	0 (0)
Hyperglycemia/new onset DM (SMQ)	68 (4)	61 (4)	23 (4)	54 (3)	50 (3)	12 (2)	33 (3)	34 (4)	6 (2)
Hypersensitivity	92 (5)	77 (5)	25 (5)	89 (5)	79 (5)	26 (5)	43 (4)	38 (5)	13 (5)
LRTI excluding pneumonia	92 (5)	79 (5)	28 (5)	77 (4)	89 (5)	30 (6)	48 (5)	42 (5)	16 (6)
Local steroid effects	183 (10)	118 (7)	33 (6)	154 (8)	119 (7)	27 (5)	59 (6)	40 (5)	9 (3)
Ocular effects	19 (1)	29 (2)	6 (1)	18 (<1)	21 (1)	6 (1)	4 (<1)	16 (2)	6 (2)
Pneumonia	102 (5)	146 (9)	64 (12)	87 (5)	146 (9)	54 (10)	36 (4)	42 (5)	17 (7)
Tremor	5 (<1)	1 (<1)	2 (<1)	0 (0)	2 (<1)	1 (<1)	4 (<1)	1 (<1)	1 (<1)
Urinary retention	1 (<1)	5 (<1)	1 (<1)	3 (<1)	4 (<1)	5 (<1)	3 (<1)	4 (<1)	2 (<1)

Data expressed as number of patients (%); BMD, bone mineral density; DM, diabetes mellitus; LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Query

On-treatment AESIs

- Rates of pneumonia and CV effects AESIs increased in the older age groups (65–74 and 75–84 years) across all treatment arms (**Table 2**).
  - Pneumonia AESIs were more common in the inhaled corticosteroid (ICS)-containing treatment arms (FF/UMEC/VI and FF/VI) than with UMEC/VI in all age categories; however, this difference did not increase with advancing age.

Conclusions

- Within each treatment group, there was no notable difference in the overall incidence of AEs by age.
- Pneumonia AESIs rates were higher in the ICS-containing arms compared with UMEC/VI and increased with increasing age, as would be anticipated.
- The safety profile of FF/UMEC/VI was as expected for patients with COPD and increasing age, and consistent with the extensive safety database of the component treatments.

References

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