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Fluticasone furoate/ umeclidinium/vilanterol (COPD) –

Addendum to Commission A18-15[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CAT	COPD Assessment Test
COPD	chronic obstructive pulmonary disease
FF	fluticasone furoate
FF/UMEC/VI	fluticasone furoate/umeclidinium/vilanterol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICS	inhaled corticosteroid
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting β2 adrenergic receptor agonist
LAMA	long-acting muscarinic receptor antagonist
PT	preferred terms
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St. George's Respiratory Questionnaire
SOC	system organ classes
UMEC	umeclidinium
VI	vilanterol

1 Background

On 9 July 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A18-15 (Fluticasone furoate/umeclidinium/vilanterol – Benefit assessment according to §35a Social Code Book V) [1].

The pharmaceutical company (hereinafter referred to as "the company") presented the results of the randomized controlled 3-arm study IMPACT on the comparison of the triple combination fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with UMEC/VI or FF/VI in its dossier [2]. For the benefit assessment, the company used the subpopulation of patients whose disease was inadequately controlled under treatment with inhaled corticosteroids (ICS) and a long-acting β2 adrenergic receptor agonist (LABA) (ICS + LABA) and who still had symptoms of the chronic obstructive pulmonary disease (COPD) such as exacerbations. Moreover, the company exclusively investigated the comparison of FF/UMEC/VI with UMEC/VI. This study was not included in the benefit assessment because the appropriate comparator therapy (ACT) - individual treatment optimization in accordance with physician's choice – under consideration of the prior therapy – with LABA and a long-acting muscarinic receptor antagonist (LAMA) and possibly ICS, was not sufficiently implemented in the comparator arm of the IMPACT study used by the company.

In its comments [3], the company presented sensitivity analyses which, from the company's point of view, showed that this treatment switch in the comparator arm caused no increased incidence of exacerbations through the abrupt discontinuation of ICS, and that the ACT (individual treatment optimization) was therefore implemented. Moreover, the company presented analyses of the adverse events (AEs) at the level of the system organ classes (SOC) and the preferred terms (PT). The G-BA commissioned IQWiG to assess these subsequently submitted analyses.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Sensitivity analyses on the effects of the abrupt discontinuation of ICS in the comparator arm

Regarding the ACT, the G-BA specified that individual treatment optimization was to comprise the substance classes LABA and LAMA, whereas ICS was only indicated as an adjunct, if appropriate. As described in the dossier assessment, ongoing symptoms and the history of exacerbations of the patients included in the IMPACT study despite pre-treatment with ICS + LABA suggest that there was the indication for an ICS + LABA + LAMA combination therapy at the start of the study at least for some of the patients. This was not implemented in the comparator arm. Instead, switching to ICS-free study medication in the comparator arm resulted in a de-escalation of the treatment that had already been inadequate at this time point despite administration of ICS. However, abrupt discontinuation of ICS can favour exacerbations. Therewith, it is altogether doubtful whether the patients included in the comparator arm UMEC/VI of the IMPACT study received adequate treatment.

To show that abrupt discontinuation of ICS in the comparator arm did not result in an increased incidence of exacerbations in the first 4 weeks under the study medication and the ACT can thus be regarded as implemented, the company presented various sensitivity analyses in its comments: an analysis of the annual exacerbation rate without consideration of exacerbations within the first 28 days, analyses on "symptoms" (COPD Assessment Test [CAT] score) and "health-related quality of life" (St. George`s Respiratory Questionnaire [SGRQ]) in the first 4 weeks as well as on the time to treatment discontinuation and time to study discontinuation.

These analyses presented by the company are assessed below.

Analyses on exacerbations

In order to demonstrate the impact the exacerbations of the first 4 weeks exerted on the result of the annual exacerbation rate in the entire course of the study, the company presented analyses on the annual exacerbation rate under exclusion of the exacerbations that had occurred until day 28. It argued that the exclusion of early exacerbations did not result in a relevant change of the treatment effect of FF/UMEC/VI and that the analyses did therefore not support the conclusion in the dossier assessment stating that abrupt discontinuation of ICS might favour exacerbations.

The analyses presented by the company are not suitable to invalidate the argument that abrupt discontinuation of ICS results in an increased incidence of exacerbations at the start of the study. This would at least require analyses of the exacerbations of the first weeks and a comparison of the exacerbations before and after day 28. The company did not present this type of analyses, however.

The analyses (without consideration of exacerbations in the first 28 days) subsequently submitted by the company included only those patients who had been at risk for at least 1 day after the first 28 days. The proportion of patients excluded from the analyses differed between

the comparator arm UMEC/VI and the intervention arm FF/UMEC/VI (5% vs. 1.4%). For the remaining patients, the exacerbation rate improved notably in the comparator arm versus the intervention arm (−10% vs −4%). This even implies that the incidence of early exacerbations was higher in the comparator arm UMEC/VI than under treatment with FF/UMEC/VI.

The presented analyses could at most be used to support the conclusion that the effect on the exacerbations shown in the study remains unchanged when the early exacerbations are not considered. But even this conclusion would only be acceptable under the assumption that individual exacerbations are independent from each other. Instead, it must be assumed that patients who already showed exacerbations at the beginning of an inadequate treatment are more likely to experience an increased incidence of exacerbations in the further course of the study [4,5].

The analyses presented by the company can thus not be interpreted against the background of the question of whether abrupt discontinuation of ICS resulted in an increased incidence of exacerbations in the patients of the comparator arm of the IMPACT study; they were not considered further. The analyses submitted by the company are shown in Appendix A of the full dossier assessment.

Analyses on “symptoms” and “health-related quality of life”

In its comment, the company submitted analyses of the mean change in the CAT score and in the SGRQ total score at week 4 to show that no direct negative effect on “health-related quality of life” (measured with the SGRQ) and “symptoms” (measured with CAT) can be found after randomization. These are shown in Table 1. The Appendix of the comment also comprises responder analyses on CAT and SGRQ at week 4. These are shown in Table 2.

Table 1: Results (morbidity and health-related quality of life at week 4, continuous) – randomized controlled trial (RCT), direct comparison: FF/UMEC/VI vs. UMEC/VI

Study Outcome category	FF/UMEC/VI			UMEC/VI			FF/UMEC/VI vs. UMEC/VI
Outcome	**N[a]**	**Values at baseline mean (SD)**	**Change at week 4 mean (SE)[b]**	**N[a]**	**Values at baseline mean (SD)**	**Change at week 4 mean (SE)[b]**	**MD [95% CI]; p-value[b] Hedges' g [95% CI][c]**
IMPACT							
Morbidity							
CAT score at week 4	1152	18.0 (7.0)	−1.5 (0.2)	530	17.5 (7.0)	−0.8 (0.2)	−0.7 [−1.2; −0.2] 0.007 −0.14 [−0.24; −0.03]
Health-related quality of life							
SGRQ total score at week 4	1178	50.4 (17.5)	−4.2 (0.3)	542	49.0 (17.7)	−2.6 (0.5)	−1.6 [−2.7; −0.5] 0.005 −0.15 [−0.25; −0.04]

a: Number of patients considered in the analysis for the calculation of the effect; the values at baseline may be based on other patient numbers.
b: MMRM with the covariables "treatment group", "smoking status", "geographical region", "visit", "baseline" and the interaction terms for "baseline" and "visit" as well as for "treatment group" and "visit".
c: Institute's calculation.

CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; CI: confidence interval; FF: fluticasone furoate; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SGRQ: St. George`s Respiratory Questionnaire; SE: standard error; vs.: versus

Table 2: Results (morbidity and health-related quality of life at week 4, responder analyses) – RCT, direct comparison: FF/UMEC/VI vs. UMEC/VI

Study Outcome category Outcome	FF/UMEC/VI N	FF/UMEC/VI Patients with event n (%)	UMEC/VI N	UMEC/VI Patients with event n (%)	FF/UMEC/VI vs. UMEC/VI RR [95% CI]; p-value[a]
IMPACT					
Morbidity (at week 4)					
COPD symptoms					
CAT responder[b]	1220	562 (46)	576	221 (38)	1.20 [1.06; 1.35]; 0.002
Health-related quality of life (at week 4)					
SGRQ responder[c]	1220	585 (48)	576	215 (37)	1.28 [1.14; 1.45]; < 0.001

a: Institute's calculation of RR. CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]).
b: Patients with a reduction of the CAT score by ≥ 2 points (reduction of the score indicates improvement). Patients with missing values at baseline or at the date of analysis were rated as non-responders.
c: Patients with a reduction in SGRQ total score by ≥ 4 points (a reduction in score indicates improvement). Patients with missing values at baseline or at the date of analysis were rated as non-responders.
CAT: COPD Assessment Test; CI: confidence interval; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SGRQ: St. George`s Respiratory Questionnaire; UMEC: umeclidinium; vs.: versus; VI: vilanterol

Based on the mean changes up to week 4, the company argued that "symptoms" and "health-related quality of life" had improved in both study arms and that there were no relevant differences at week 4 between patients who had discontinued ICS (UMEC/VI arm) and those whose ICS treatment had been continued (FF/VI); thus, discontinuation of ICS obviously entailed no deterioration of the quality of life.

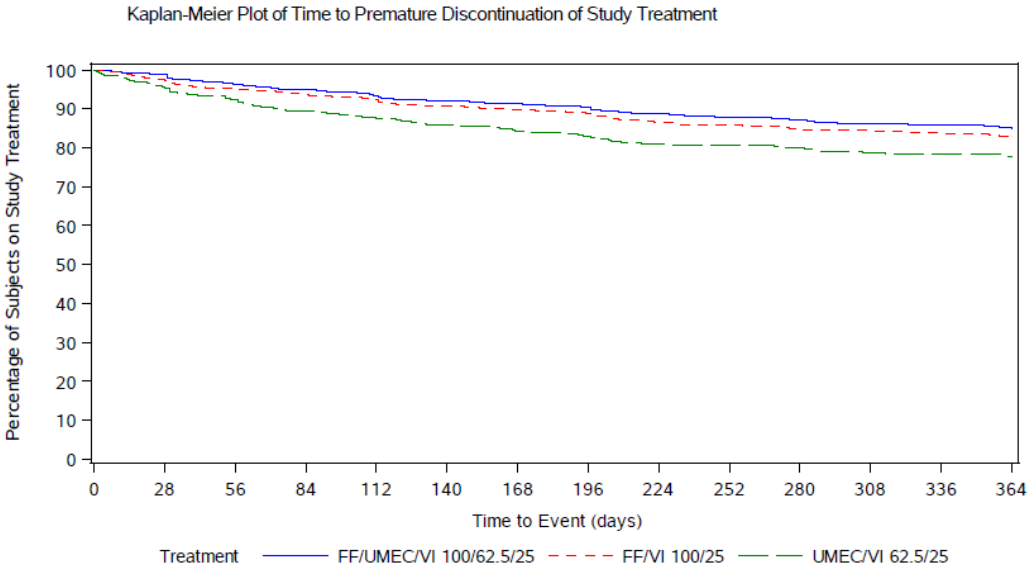
This rationale was not followed. At first, it must be taken into account that all patients included in the subpopulation had been pretreated with a combination of LABA and ICS, which provided inadequate control of their COPD and resulted in further incidences of symptoms including exacerbations. The FF/VI arm, which, for the patients, meant continuation of their inadequate treatment with ICS + LABA, was therefore not meaningfully interpretable with regard to the research question of whether abrupt discontinuation of ICS results in an increased incidence of exacerbations. The results on the FF/VI arm are therefore not considered further.

Relevant differences between the triple combination (FF/UMEC/VI) and the UMEC/VI arm regarding the mean change in the CAT score and the SGRQ total score at week 4 were not found under consideration of Hedges' g. However, considering the responder analyses it becomes clear that the effect is already present at week 4 both for "symptoms" and for "health-

related quality of life". These results can most likely be interpreted as refutation of the company's argumentation.

Time to treatment or study discontinuation

As further sensitivity analysis, the company presented Kaplan-Meier curves on the time to treatment discontinuation (Figure 1) or on the time to study discontinuation (Figure 2) in the subpopulation of patients who had been pretreated with ICS + LABA.



Number of Subjects on Treatment

FF/UMEC/VI 100/62.5/25	1220	1205	1176	1159	1140	1122	1114	1103	1082	1071	1064	1051	1047	764
FF/VI 100/25	1177	1149	1122	1103	1088	1066	1058	1046	1019	1010	999	993	985	710
UMEC/VI 62.5/25	576	551	532	516	505	494	486	477	467	465	461	453	451	312

Note: Kaplan-Meier estimate of time to premature discontinuation of study treatment. Subjects are represented from their Day 1 date to the date of last dose of study treatment (or date of death). Subjects that complete the treatment period per protocol are censored at the earliest of date of last dose of study treatment and day 365.

Figure 1: Kaplan-Meier curve on the time to treatment discontinuation, IMPACT study

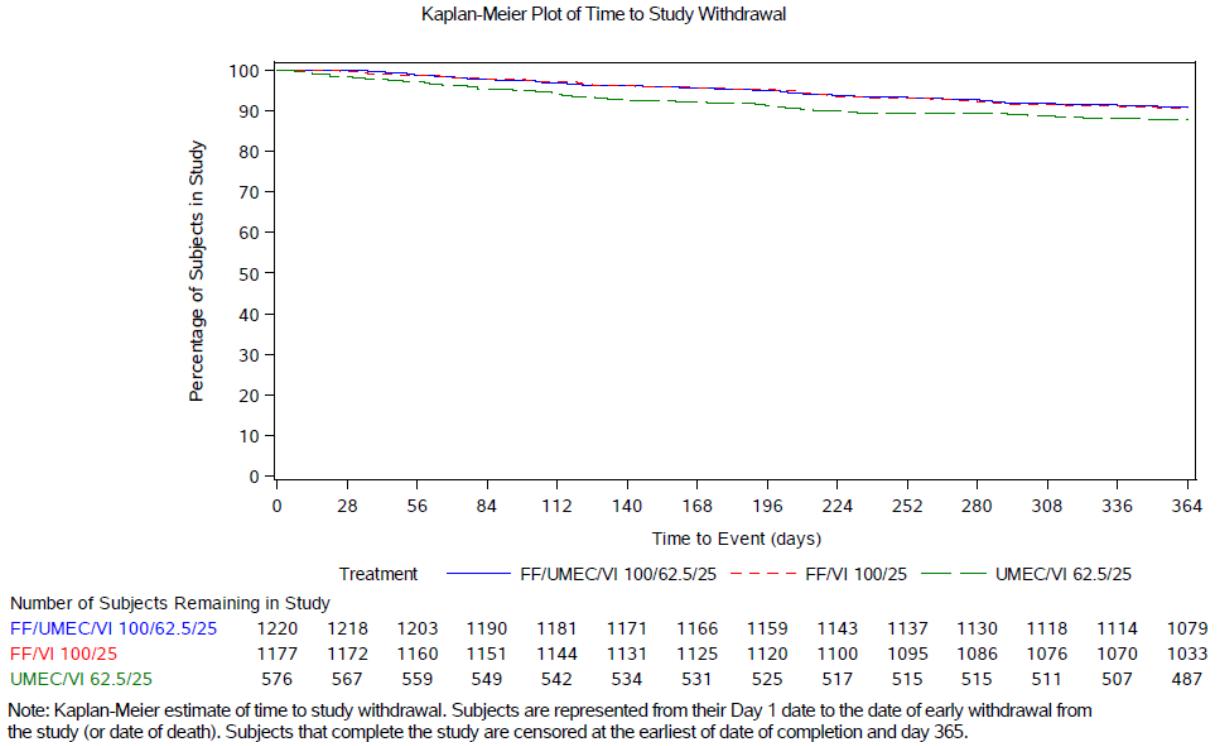


Figure 2: Kaplan-Meier curve on the time to study discontinuation, IMPACT study

From the company's point of view, it could not be ascertained whether patients who discontinued treatment with ICS (UMEC/VI) differed from those patients who continued their ICS treatment (FF/VI) with regard to the early treatment or study discontinuation.

During the first 28 days, no noticeable differences were found between the treatment arms UMEC/VI and FF/VI regarding the outcomes "time to treatment discontinuation" or "time to study discontinuation". However, it must be taken into account that according to the study protocol discontinuation of the treatment or the study was not foreseen in case of exacerbations. There is thus no direct connection between the occurrence of exacerbations and treatment or study discontinuation. In the further course of the study, a tendency towards an increase of patients who discontinued the treatment or the study was observed in the UMEC/VI treatment arm. Data on the number of patients who discontinued treatment or study due to exacerbations are neither available for the first 4 weeks nor for the entire course of the study. The data are therefore not interpretable.

Conclusions

Overall, the sensitivity analyses presented by the company with the comment are unsuitable to invalidate the conclusion of the dossier assessment stating that abrupt discontinuation of ICS might have resulted in an increased incidence of exacerbations in the IMPACT study. The presented analyses are either not interpretable in this regard (exacerbations, time to treatment or study discontinuation) or they speak rather against the company's argumentation (analyses on "symptoms" and "health-related quality of life").

Irrespective of this, it must be noted that through the discontinuation of ICS some of the patients in the comparator arm UMEC/VI of the study possibly received inadequate treatment not only at the start of the study, but also over the entire course of the study.

Informative data could only be obtained via comparison with an additional study arm in which patients were actually switched to individual treatment with LABA + LAMA or LABA + LAMA + ICS in accordance with the ACT.

It therefore remains unclear whether LABA + LAMA presented adequate treatment in the sense of individual treatment optimization of the ACT for the patients in the comparator arm.

2.2 Analysis of the AEs at SOC/PT level

For the IMPACT study, the company subsequently submitted analyses of the AEs at SOC/PT level for the relevant subpopulation of the patients pretreated with ICS + LABA. The common AEs, serious AEs (SAEs) and discontinuations due to AEs are shown in Table 5 to Table 7 in Appendix A.

No relevant specific AEs for the assessment of FF/UMEC/VI in comparison with the ACT were identified on the basis of these analyses.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of FF/UMEC/VI from dossier assessment A18-15.

The following Table 3 shows the result of the benefit assessment of FF/UMEC/VI under consideration of dossier assessment A18-15 and the present addendum.

Table 3: FF/UMEC/VI – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Maintenance treatment in adults with moderate to severe COPD inadequately controlled with a combination of one ICS and one LABA[b]	Individual treatment optimization in accordance with physician's choice – under consideration of the previous therapy – with LABA and LAMA and possibly ICS	Added benefit not proven
a: Presentation of the ACT specified by the G-BA. b: It is assumed that COPD in patients for whom treatment with the drug combination FF/UMEC/VI was an option, was inadequately controlled with the previous therapy and the patients still had symptoms (including exacerbations). COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; G-BA: Federal Joint Committee; ICS: inhaled corticosteroid; LABA: long-acting β2 adrenergic receptor agonist; LAMA: long-acting muscarinic receptor antagonist; UMEC: umeclidinium; VI: vilanterol		

The G-BA decides on the added benefit.

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Appendix A– Sensitivity analyses on exacerbations of the IMPACT study

Table 4: Results (morbidity - exacerbations excluding exacerbations until day 28) – RCT, direct comparison: FF/UMEC/VI vs. UMEC/VI

Study Outcome category Outcome	FF/UMEC/VI N	FF/UMEC/VI Annual exacerbation rate: [95 % CI]	UMEC/VI N	UMEC/VI Annual exacerbation rate: [95 % CI]	FF/UMEC/VI vs. UMEC/VI Rate ratio [95 % CI]; p-value[a]
IMPACT					
Morbidity					
Annual exacerbation rate[b]					
moderate or severe exacerbations	1200[c]	0.68 [0.62; 0.75]	547[c]	0.84 [0.74; 0.96]	0.81 [0.69; 0.95]; 0.010
severe exacerbations		ND		ND	ND

a: Negative binomial model adjusted for sex, exacerbations in the year before study participation, smoking status, geographical region and FEV1 % target on day 1.
b: Exacerbations starting before or on day 28 are excluded.
c: The analyses included only patients who had been at risk for at least 1 day after the first 28 days. Patients who had discontinued the study within the first 28 days were not included.

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; UMEC: umeclidinium; vs.: versus; VI: vilanterol

Appendix B – Results on side effects of the IMPACT study

Table 5: Common AEs (in the SOC or in the PT ≥ 2 % in at least one study arm) – RCT, direct comparison: FF/UMEC/VI vs. UMEC/VI

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**FF/UMEC/VI** **N = 1220**	**UMEC/VI** **N = 576**
IMPACT		
Overall rate of AEs	799 (65)	378 (66)
Infections and infestations	492 (40)	214 (37)
Viral upper respiratory tract infection	152 (12)	56 (10)
Upper respiratory tract infection (not specified in detail)	82 (7)	35 (6)
Pneumonia	81 (7)	20 (3)
Bronchitis	56 (5)	31 (5)
Influenza	38 (3)	13 (2)
oral candidiasis	33 (3)	12 (2)
Pharyngitis	28 (2)	17 (3)
Urinary tract infection	24 (2)	12 (2)
Respiratory, thoracic and mediastinal disorders	243 (20)	133 (23)
Chronic obstructive pulmonary disease	112 (9)	74 (13)
Cough	33 (3)	17 (3)
Musculoskeletal and connective tissue disorders	152 (12)	62 (11)
Back pain	32 (3)	16 (3)
Arthralgia	28 (2)	9 (2)
Gastrointestinal disorders	137 (11)	63 (11)
Diarrhoea	27 (2)	16 (3)
Nervous system disorders	126 (10)	38 (7)
Headache	67 (5)	26 (5)
General disorders and administration site conditions	70 (6)	41 (7)
Injury, poisoning and procedural complications	67 (5)	24 (4)
Cardiac disorders	68 (6)	25 (4)
Metabolism and nutrition disorders	52 (4)	34 (6)
Skin and subcutaneous tissue disorders	46 (4)	19 (3)
Investigations	38 (3)	26 (5)
Psychiatric disorders	41 (3)	15 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	22 (2)	12 (2)

a: MedDRA version 20.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 6: Common SAEs (in the SOC or in the PT ≥ 1 % in at least one study arm) – RCT, direct comparison: FF/UMEC/VI vs. UMEC/VI

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**FF/UMEC/VI** **N = 1220**	**UMEC/VI** **N = 576**
IMPACT		
Overall rate of SAEs	207 (17)	102 (18)
Respiratory, thoracic and mediastinal disorders	111 (9)	69 (12)
Chronic obstructive pulmonary disease	102 (8)	68 (12)
Infections and infestations	57 (5)	19 (3)
Pneumonia	44 (4)	13 (2)
Cardiac disorders	26 (2)	7 (1)

a: MedDRA version 20.0.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 7: Common AEs leading to study discontinuation (in the SOC or in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: FF/UMEC/VI vs. UMEC/VI

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**FF/UMEC/VI** **N = 1220**	**UMEC/VI** **N = 576**
IMPACT		
Overall rate of discontinuations due to AEs	49 (4)	48 (8)
Respiratory, thoracic and mediastinal disorders	24 (2)	28 (5)
Chronic obstructive pulmonary disease	18 (1)	21 (4)
Infections and infestations	11 (< 1)	7 (1)
Cardiac disorders	5 (< 1)	6 (1)

a: MedDRA version 20.0.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus