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An Analysis of the IMPACT Trial Assessing Single-Inhaler Therapy With Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Versus FF/VI and UMEC/VI Using a Composite Adverse Event Outcome in Patients With COPD

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Recording by J Michael Wells

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Objectives

- The IMPACT trial demonstrated that FF/UMEC/VI single-inhaler triple therapy significantly reduced severe exacerbation rates and all-cause mortality risk versus UMEC/VI in patients with symptomatic COPD at risk of exacerbations.[1]
- Concerns have been raised about an increased risk of pneumonia with ICS-containing regimens as well as CV effects with dual bronchodilation.[2,3]
- This post hoc analysis aims to evaluate the benefit–risk profile of FF/UMEC/VI versus FF/VI and UMEC/VI in the IMPACT population by means of a cardiopulmonary composite endpoint including on-treatment exacerbations, pneumonia, CV events, and death.

CV, cardiovascular; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids FF, fluticasone furoate; HR, hazard ratio; UMEC, umeclidinium; VI, vilanterol

1. Lipson DA, et al. N Engl J Med 2018;378:1671–80; 2. Finney L, et al. Lancet Respir Med 2014;2:919–32; 3. Rabe et al., Eur Respir Rev 2018; 27:180057.
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Methods

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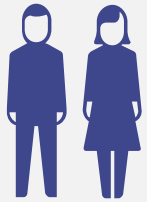
Study[1]

Randomized | Double-blind | Multicenter

Phase III

(CTT116855 [NCT02164513])

Patients[1]



≥40 years of age

Symptomatic COPD: CAT score ≥10 at screening

FEV_1 <50% predicted at screening and ≥1 moderate/severe exacerbation* in prior 12 months

OR

FEV_1 50–<80% at screening and ≥2 moderate or ≥1 severe exacerbation in prior 12 months

Treatments[1]

2 : 2 : 1 randomization
FF/UMEC/VI : FF/VI : UMEC/VI

FF/UMEC/VI
Once daily
Fluticasone furoate 100 mcg
Umeclidinium 62.5 mcg
Vilanterol 25 mcg

FF/VI
Once daily
Fluticasone furoate 100 mcg
Vilanterol 25 mcg

UMEC/VI
Once daily
Umeclidinium 62.5 mcg
Vilanterol 25 mcg

52 weeks

Post hoc analysis

Time-to-first composite adverse event in patients treated with FF/UMEC/VI versus FF/VI and UMEC/VI

Events included in the analysis:

- on-treatment severe exacerbations
- **OR**
- on-treatment cardiovascular AESI resulting in hospitalization or death
- **OR**
- on-treatment pneumonia AESI resulting in hospitalization or death
- **OR**
- on-treatment death from any cause

Patients with multiple events: only the first event (chronologically) contributed to this analysis

Analyzed using a Cox proportional hazards model†

*Moderate exacerbation, any exacerbation requiring antibiotics and/or oral/systemic corticosteroids; severe exacerbation, any exacerbation leading to hospitalization or death; †covariates: treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), geographical region, smoking status (screening), and post-bronchodilator percent predicted FEV_1 (screening).

AESI, adverse event of special interest; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

1. Lipson DA, et al. N Engl J Med 2018;378:1671–80.

Wells JM, et al. An Analysis of the IMPACT Trial Assessing Single-Inhaler Therapy With Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) Versus FF/VI and UMEC/VI Using a Composite Adverse Event Outcome in Patients With COPD.

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Baseline characteristics and demographics were similar between treatment groups (ITT population)

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	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)	Total (N=10,355)
Age, mean (SD) years	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)	65.3 (8.3)
Sex (male), n (%)	2766 (67)	2748 (66)	1356 (66)	6870 (66)
BMI*, mean (SD) kg/m^2	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)	26.6 (6.1)
Former smoker at screening, n (%)	2715 (65)	2711 (66)	1342 (65)	6768 (65)
Exacerbation history in prior 12 months†, n (%)				
1 moderate/severe exacerbation	1853 (45)	1907 (46)	931 (45)	4691 (45)
2 moderate/severe exacerbations	1829 (44)	1768 (43)	890 (43)	4487 (43)
≥2 moderate/severe exacerbation	2296 (55)	2222 (54)	1137 (55)	5655 (55)
Any CV risk factor at screening‡, n (%)	2786 (67)	2812 (68)	1414 (68)	7012 (68)
Past history of pneumonia§, n (%)	916 (22)	951 (23)	476 (23)	2343 (23)
Post-bronchodilator FEV_1 % predicted¶, mean (SD)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)	45.5 (14.8)

*FF/UMEC/VI, n=4148; FF/VI, n=4134; UMEC/VI, n=2070; total, n=10,352; †moderate exacerbations were any exacerbations requiring antibiotics and/or oral/systemic corticosteroids, severe exacerbations were any exacerbations leading to hospitalization or death; ‡CV risk factors included past or current history of: angina pectoris; coronary artery disease; myocardial infarction; arrhythmia; congestive heart failure; hypertension; cerebrovascular accident; carotid or aorto-femoral vascular disease; diabetes mellitus; hypercholesterolemia; §any history of pneumonia; ¶FF/UMEC/VI, n=4145; FF/VI, n=4133; UMEC/VI, n=2069; total, n=10,347.
BMI, body mass index; CV, cardiovascular; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol

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Looking at all events, severe exacerbations were the most frequent of the composite components

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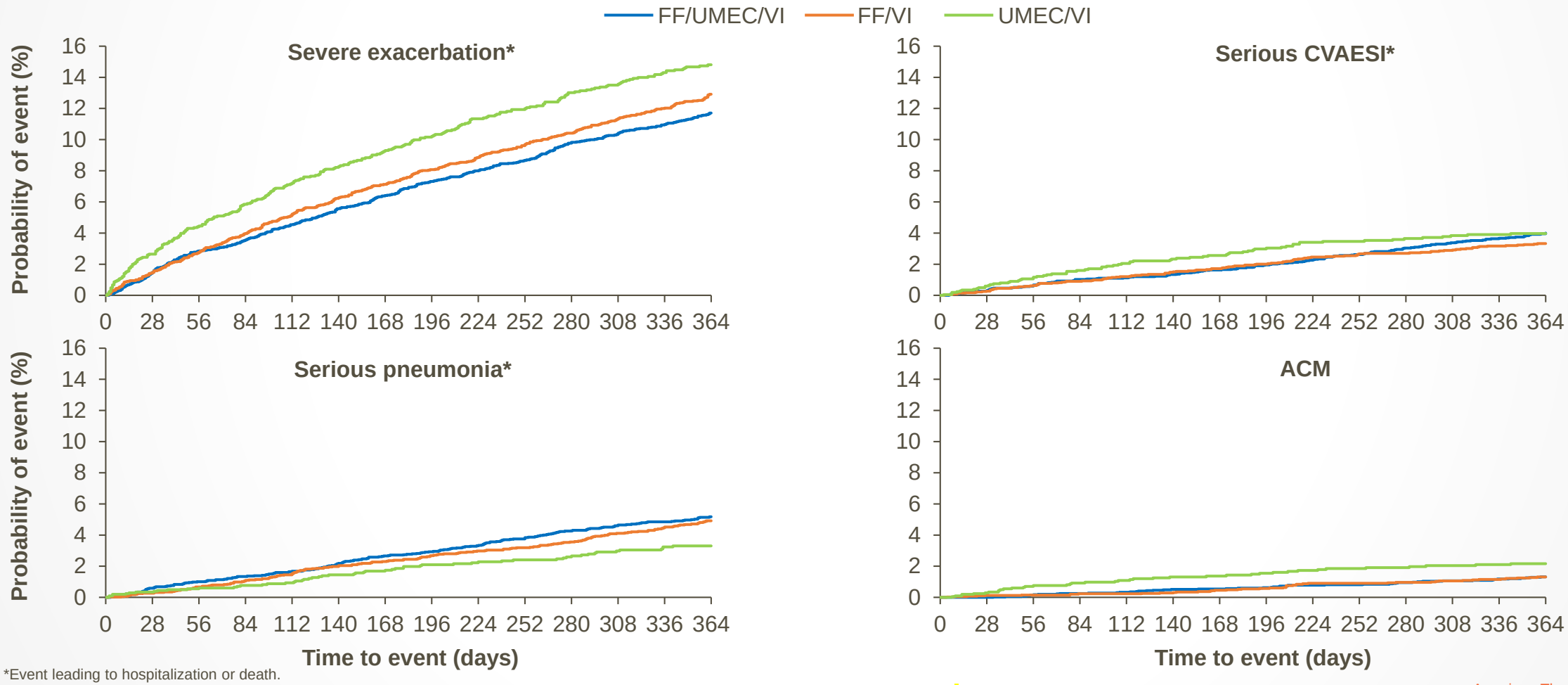
Independent events Kaplan–Meier plots, irrespective of whether a patient had any of the other events at any time.



*Event leading to hospitalization or death.
ACM, all-cause mortality; CVAESI, cardiovascular adverse event of special interest; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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Looking at first events only, severe exacerbations were the main driver of the composite endpoint

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Incidence of the composite endpoint components, considering only the first of the events that occur*.

	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
On-treatment ACM, severe exacerbation, serious pneumonia AESI, or serious CVAESI, n	647	636	356
Composite component, n (%)*			
Severe exacerbation†	428 (66)	445 (70)	264 (74)
Serious CVAESI†	120 (19)	100 (16)	60 (17)
Serious pneumonia AESI†	165 (26)	125 (20)	44 (12)
ACM	27 (4)	29 (5)	23 (6)

*Table details the number (%) of patients with first events in the analysis of the composite endpoint. If a patient experienced more than one of these events on the same day, they are included in applicable categories. If a patient experienced more than one of these events on different days, they are included in the category that occurred first; †event leading to hospitalization or death.
ACM, all-cause mortality; AESI, adverse event of special interest; CVAESI, cardiovascular adverse event of special interest; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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FF/UMEC/VI significantly reduced the risk of an on-treatment composite adverse event versus UMEC/VI

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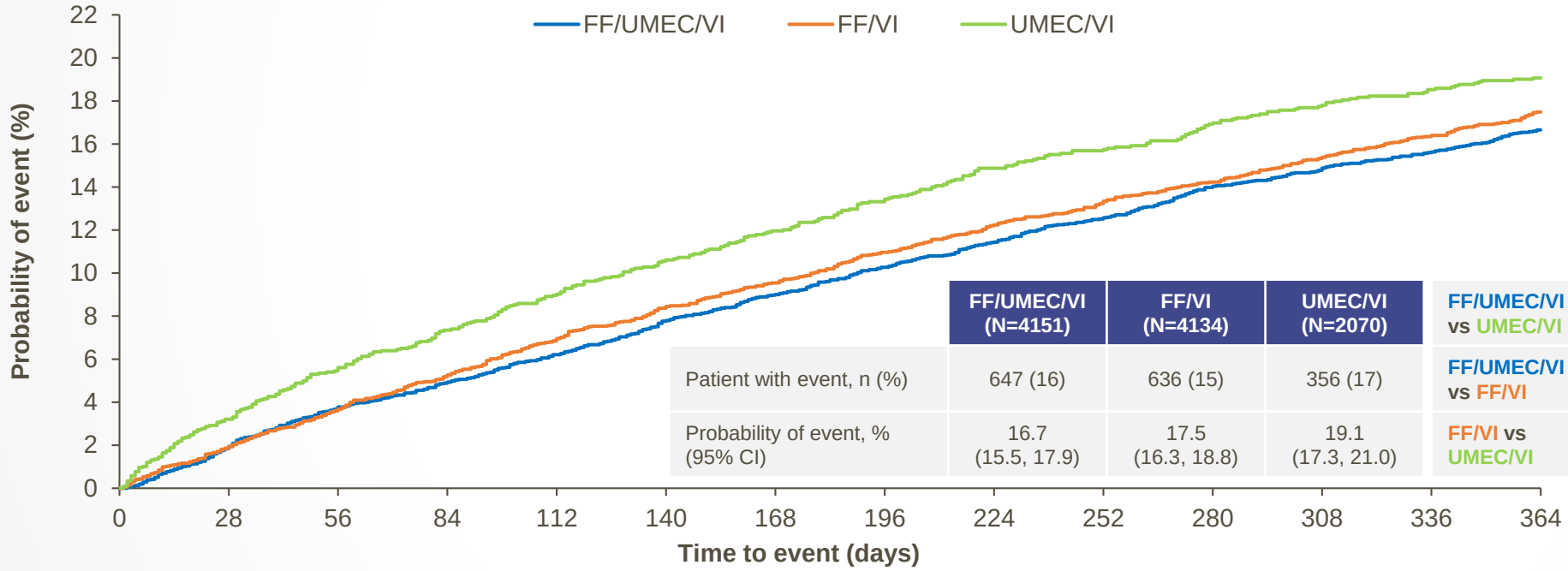
TIME-TO-FIRST ON-TREATMENT SEVERE EXACERBATION OR SERIOUS PNEUMONIA OR SERIOUS CVAESI OR ACM

- FF/UMEC/VI significantly reduced composite event risk by 16.5% versus UMEC/VI. The point estimates for the reduction in the risk of a composite event favored FF/UMEC/VI over FF/VI and FF/VI over UMEC/VI but were not statistically significant.



	FF/UMEC/VI (N=4151)	FF/VI (N=4134)	UMEC/VI (N=2070)
Patient with event, n (%)	647 (16)	636 (15)	356 (17)
Probability of event, % (95% CI)	16.7 (15.5, 17.9)	17.5 (16.3, 18.8)	19.1 (17.3, 21.0)

	HR (95% CI)	Risk reduction, % (95% CI)	*P*-value
FF/UMEC/VI vs UMEC/VI	0.83 (0.73, 0.95)	16.5 (5.0, 26.7)	**0.006**
FF/UMEC/VI vs FF/VI	0.94 (0.84, 1.05)	6.2 (-4.7, 15.9)	0.255
FF/VI vs UMEC/VI	0.89 (0.78, 1.01)	11.1 (-1.3, 21.9)	0.077

Number of patients at risk

FF/UMEC/VI	4151	4014	3850	3746	3652	3529	3460	3398	3301	3238	3165	3101	3053	2930
FF/VI	4134	3924	3689	3552	3434	3284	3208	3124	3015	2959	2911	2841	2796	2672
UMEC/VI	2070	1948	1818	1740	1676	1607	1564	1526	1467	1441	1412	1378	1356	1309

ACM, all-cause mortality; CI, confidence interval; CVAESI, cardiovascular event of special interest; FF, fluticasone furoate; HR, hazard ratio; UMEC, umeclidinium; VI, vilanterol

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Conclusions

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- FF/UMEC/VI statistically significantly reduced the risk of a composite event comprising on-treatment severe exacerbations, serious pneumonia, serious CVAESI, or death by 16.5% compared with UMEC/VI.
  - The point estimates favored FF/UMEC/VI over FF/VI and FF/VI over UMEC/VI but were not statistically significant.
- Of the individual composite components included in this analysis severe exacerbations were the most frequent and main driver of the composite adverse event.
- These results demonstrate the favorable benefit–risk profile of once-daily FF/UMEC/VI triple therapy compared with dual therapy in patients with symptomatic COPD and a history of exacerbations.

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COPD, chronic obstructive pulmonary disease; CVAESI, cardiovascular event of special interest; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

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CO-AUTHORS' DISCLOSURES

- SP Bhatt has received personal fees from GSK and Sunovion; research support from Sanofi; grant support from NIH. TF Carr has received personal fees from Aimmune, AstraZeneca, GSK, Novartis, Sanofi Genzyme, and Regeneron. GJ Criner has received personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, CSA Medical, Eolo, GSK, Novartis, Nuvaira, Olympus, Pulmonx, Verona, Amgen, Broncus Medical, Gala Therapeutics, Helios Medical, Medtronic, Merck, Mereo Biopharma, NGM Pharmaceuticals, Philips Respironics, Respivant Sciences, and The Implementation Group; he has ownership interest in HGE technologies. DMG Halpin has received personal fees from AstraZeneca, Chiesi, GSK, Pfizer, and Sanofi; personal fees and nonfinancial support from Boehringer Ingelheim and Novartis. MK Han has received personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Mylan, Merck, Verona, and Teva; research support from Novartis and Sunovion. R Jain, DA Lipson, and D Midwinter are employees of GSK and hold stocks and shares in GSK. MG Kaye has nothing to disclose. M Kraft has received personal fees for consulting in asthma from AstraZeneca, Sanofi, Genentech, and Chiesi; research support from NIH, ALA, AstraZeneca, Sanofi, and Chiesi, and is cofounder of RaeSedo, LLC, a company that studies peptidomimetics for treatment of asthma. D Mapel has received research grant funding from AstraZeneca, Boehringer Ingelheim, Endo Pharmaceuticals, GSK, Sunovion, and Pfizer Pharmaceuticals; personal fees from Mylan/Theravance, and Biopharma. MJ Mammen has nothing to disclose. C McEvoy has received clinical trial support from GSK, AstraZeneca, and Respirtech/Philips; grant support from NIH, Department of Defense, Respirtech/Philips and Virgilant; personal consulting fees from Virgilant. D Singh has received personal fees from GSK, Cipla, Genentech, and Peptinnovate; personal fees and grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Menarini, Mundipharma, Novartis, Pfizer, Pulmatrix, Theravance, and Verona. R Wise has received personal fees and grant support from AstraZeneca, Boehringer Ingelheim, and GSK; personal fees from Contrafect, Pulmonx, Roche, Sunovion, Merck, Circassia, Pneuma, Verona, Mylan/Theravance, Propeller Health, AbbVie, Kiniksa, Galderma, Kinevant, Chimerx, Puretech, and Kamada; grant support from Pearl Therapeutics and Sanofi-Aventis. MT Dransfield has received personal fees and contracted clinical trial support from Boehringer Ingelheim, GSK, AstraZeneca, and PneumRx/BTG; personal fees from Quark Pharmaceuticals; grant support from American Lung Association, Department of Defense, Department of Veterans Affairs, and NIH; contracted clinical trial support from Novartis, Yungjin, Pulmonx, Boston Scientific, Gala, and Nuvaira.