Once-Daily Single-Inhaler Versus Twice-Daily Multiple-Inhaler Triple Therapy: Two Replicate Trials in Patients With Chronic Obstructive Pulmonary Disease (COPD)

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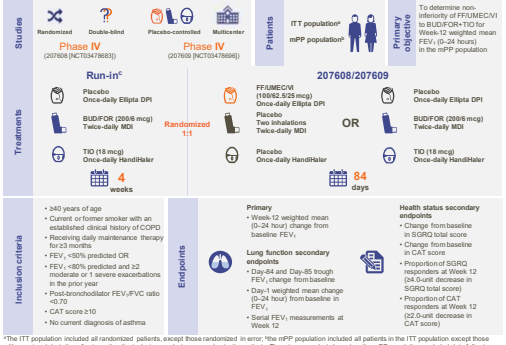
Introduction

- Until recently, inhaled triple therapy for patients with chronic obstructive pulmonary disease (COPD) has required the administration of multiple inhalers, several times a day. However, outside of the clinical trial environment, adherence to inhaled therapy for COPD is generally low.[1] Recently, single-inhaler triple therapies have been developed that may offer advantages over multiple-inhaler use, with studies suggesting that simplifying treatment with a single inhaler may increase therapy adherence resulting in improved health outcomes due to a reduction in treatment discontinuation.[1–4]
- Once-daily single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) has demonstrated efficacy benefits versus dual therapy with UMEC/VI or FF/VI.[5] However, the comparative efficacy and safety of single-inhaler triple therapy with FF/UMEC/VI versus multiple-inhaler triple therapy with inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) has not been evaluated.
- This analysis reports on two replicate trials comparing the efficacy and safety of FF/UMEC/VI versus budesonide/formoterol plus tiotropium (BUD/FOR+TIO) in patients with COPD.

Methods



[a]The ITT population included all randomized patients, except those randomized in error; [b]the mPP population included all patients in the ITT population except those with a protocol deviation of not meeting the inclusion, exclusion, or randomization criteria. The primary analysis based on the mPP population excluded data following the occurrence of these intercurrent events: discontinuation of randomized study treatment; taking the wrong randomized study treatment; taking a prohibited medication; unblinding of randomized study treatment; treatment noncompliance; moderate/severe COPD exacerbation or pneumonia; [c]during the run-in period patients discontinued existing treatments. CAT, COPD Assessment Test; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ITT, intent-to-treat; mPP, modified per protocol; SGRQ, St George's Respiratory Questionnaire.

- Endpoints were analyzed for each study separately and for the pooled ITT population.
- The primary objective was to determine non-inferiority of FF/UMEC/VI to BUD/FOR+TIO based on the mPP population and 0–24-hour weighted mean FEV_1 at Week 12. The margin of non-inferiority was 50 mL and the true mean treatment difference was assumed to be 10 mL.
- Change from baseline in weighted mean FEV_1, trough FEV_1, serial FEV_1, SGRQ total score, and CAT score were analyzed using a mixed model repeated measures analysis with covariates of baseline value, geographical region, treatment, visit, visit by treatment, and visit by baseline interactions. The proportion of SGRQ total score and CAT score responders was analyzed using a generalized linear mixed model. Safety endpoints were analyzed using descriptive statistics. The pre-specified pooled analysis of both studies was conducted using the pooled ITT population.

Results

Patients

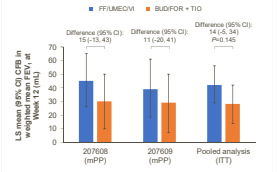
- The mPP population included 720 and 711 patients in studies 207608 and 207609 (ITT population: 728 and 732). Patient baseline demographics and clinical characteristics are described in **Table 1**.

Table 1. Patient demographics and baseline characteristics (ITT population)

	Study 207608		Study 207609	
	FF/UMEC/VI N=363	BUD/FOR+TIO N=365	FF/UMEC/VI N=366	BUD/FOR+TIO N=366
Age, years, mean (SD)	65.4 (7.9)	64.9 (8.1)	65.5 (8.2)	65.1 (8.4)
Female, n (%)	180 (50)	164 (45)	180 (49)	179 (49)
BMI, kg/m², mean	28.21 (6.58)	28.40 (6.93)	28.54 (7.56)	28.67 (7.14)
Smoking history and status				
Current smoker, n (%)	186 (51)	168 (46)	170 (46)	190 (52)
COPD history	n=363	n=365	n=366	n=365
Duration of COPD, years, mean (SD)	10.5 (6.8)	9.9 (6.8)	10.4 (7.3)	9.7 (7.0)
Exacerbation history in prior 12 months, n (%)				
≥2 moderate exacerbations	111 (31)	119 (33)	114 (31)	105 (29)
≥2 severe exacerbations	5 (1)	5 (1)	3 (<1)	9 (2)
Screening lung function, mean (SD)	n=363	n=364	n=362	n=366
Post-bronchodilator FEV_1 (L)	1.176 (0.431)	1.199 (0.411)	1.128 (0.398)	1.181 (0.429)
Post-bronchodilator FEV_1, % predicted	42.5 (11.9)	42.3 (12.3)	41.4 (12.5)	42.8 (13.0)
CAT score at screening, mean (SD)[†]	21.6 (6.5)	22.0 (6.6)	22.2 (6.3)	22.3 (6.4)

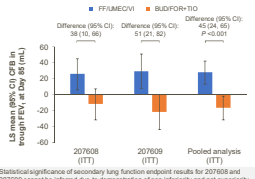
[†]207608, FF/UMEC/VI: n=359; BUD/FOR+TIO: n=364; 207609, FF/UMEC/VI: n=364; BUD/FOR+TIO: n=360. BMI, body mass index; SD, standard deviation

Figure 1. FF/UMEC/VI was non-inferior to BUD/FOR+TIO for weighted mean change from baseline in FEV_1 (0–24 hour) at Week 12 in 207608 and 207609



CFB, change from baseline; CI, confidence interval; LS, least squares

Figure 2. FF/UMEC/VI improved change from baseline in trough FEV_1 at Day 85 versus BUD/FOR+TIO in 207608 and 207609, and in the pooled analysis (ITT population)



Statistical significance of secondary lung function endpoint results for 207608 and 207609 cannot be inferred due to demonstration of non-inferiority and not superiority on the primary endpoint

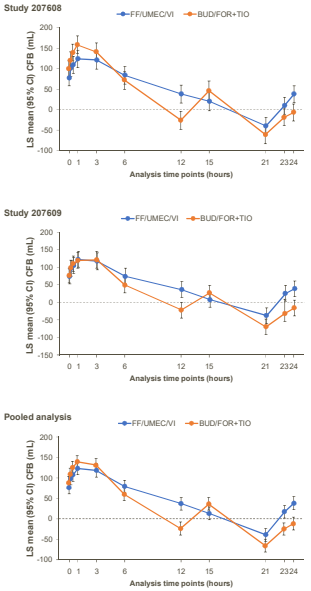
Weighted mean change from baseline in 0–24-hour FEV_1 at Day 1

- Weighted mean change from baseline in 0–24-hour FEV_1 at Day 1 was similar with FF/UMEC/VI and BUD/FOR+TIO in both studies in the mPP population (treatment difference: Study 207608: -9 [95% CI: -30, 13]; Study 207609: 4 [95% CI: -16, 23]) and in the pooled analysis ITT population (treatment difference: -3 [95% CI: -17, 11; P=0.683]).

SGRQ total score and CAT score at Week 12

- There was no significant difference for proportion of responders based on both SGRQ total score and CAT score in the pooled ITT population (odds ratio [95% CI]: SGRQ, 1.05 [0.84, 1.31]; P=0.671; CAT, 1.04 [0.83, 1.30]; P=0.732). Change from baseline in SGRQ total score and CAT score is reported in **Figure 4**.

Figure 3. FF/UMEC/VI improved serial FEV_1 measurements at Week 12 versus BUD/FOR+TIO at 12- and 24-hour time points (ITT population)



Conclusions

- Once-daily single inhaler triple therapy with FF/UMEC/VI was non-inferior to multiple inhaler therapy with twice-daily BUD/FOR and once-daily TIO on weighted mean FEV_1.
- Safety profiles were similar between treatments, with a low incidence of pneumonia seen in patients receiving FF/UMEC/VI or BUD/FOR+TIO, across both studies (<1–2% across treatment arms).
- FF/UMEC/VI improved CFB trough FEV_1 compared with BUD/FOR+TIO. These improvements indicate that FF/UMEC/VI as a once-daily single-inhaler triple therapy is a good alternative with a simplified treatment regimen compared with twice-daily multiple-inhaler therapy with BUD/FOR+TIO. Overall these data indicate that patients may be effectively switched from multiple inhaler therapy with BUD/FOR+TIO to single inhaler therapy with FF/UMEC/VI.

Figure 4. No significant treatment difference was seen in change from baseline for Week 12 in (A) SGRQ total score (B) CAT score

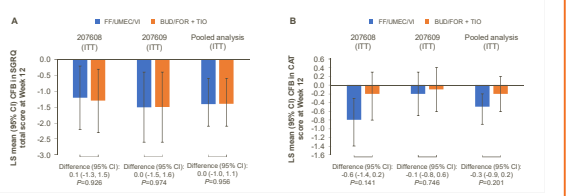


Table 2. Incidence of adverse events, serious adverse events, and adverse events of special interest were similar across treatments and both Study 207608 and 207609 (ITT population)

	Study 207608		Study 207609	
	FF/UMEC/VI N=363	BUD/FOR + TIO N=365	FF/UMEC/VI N=366	BUD/FOR + TIO N=366
Adverse events	n (%)	n (%)	n (%)	n (%)
Any	131 (36)	121 (33)	92 (25)	109 (30)
Drug-related	23 (6)	16 (4)	9 (2)	10 (3)
Leading to permanent discontinuation or withdrawal	7 (2)	7 (2)	2 (<1)	5 (1)
Serious adverse events				
Any	25 (7)	14 (4)	12 (3)	17 (5)
Drug-related	4 (1)	0	1 (<1)	1 (<1)
Leading to permanent discontinuation or withdrawal	5 (1)	5 (1)	1 (<1)	4 (1)
Fatal	0	0	0	1 (<1)
Adverse events of special interest				
Cardiovascular effects	10 (3)	8 (2)	11 (3)	8 (2)
Decreased BMD and associated fractures	5 (1)	3 (<1)	2 (<1)	4 (1)
LRTI excluding pneumonia	9 (2)	1 (<1)	1 (<1)	1 (<1)
Pneumonia	5 (1)	6 (2)	2 (<1)	3 (<1)

BMD, bone mineral density; LRTI, lower respiratory tract infection

References

1. IQVIA. Applied Patient Level Data, weekly March 2018-March 2019..
2. Bogart M, et al. *Int J Chron Obstruct Pulmon Dis* 2019;14:343–52.
3. Yu AP, et al. *J Med Econ* 2011;14:486–96.
4. van Boven JF, et al. *Respir Med* 2014; 108:103–13.
5. Lipson DA, et al. *N Engl J Med* 2018;378:1671–80.

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