Analysis of a Composite Endpoint of Exacerbation and Early Study Treatment Withdrawal in Symptomatic Patients With COPD Free of Inhaled Corticosteroids: A Post Hoc Analysis of the EMAX Trial

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EMAX TRIAL

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Background

- In COPD clinical trials, differential withdrawal rates between treatment groups can cause bias due to the healthy survivor population increasing with time.[1,2] This may lead to an underestimation of the benefits of investigational treatment.
- Treatment differences in exacerbation rate reduction have been shown to decrease over time as a result of early treatment withdrawal.[1,2]
  - A composite endpoint of exacerbation and treatment withdrawal has been developed to compensate for the impact of early treatment withdrawal on exacerbation outcomes.[2]
- This post hoc analysis of the Early MAXimization of bronchodilation for improving COPD stability (EMAX) trial examined whether there were differential treatment withdrawal rates between treatment groups and if a composite endpoint of exacerbation and study treatment withdrawal would better capture treatment benefits than the individual endpoints.

Methods

- The 24-week, double-blind, parallel-group EMAX trial randomized patients with symptomatic COPD and low exacerbation risk not receiving inhaled corticosteroids 1:1:1 to umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg once daily, UMEC 62.5 mcg once daily, or salmeterol (SAL) 50 mcg twice daily for 24 weeks. Patients were limited to a maximum or one long-acting muscarinic antagonist (LAMA) or long-acting β_2-agonist (LABA) monotherapy before screening and during run-in.[3]
- Time to first moderate or severe exacerbation was analysed a priori. Time to study treatment withdrawal and the composite endpoint of time to first moderate or severe exacerbation and time to study treatment withdrawal were analyzed post hoc.
- Hazard ratios (HR) and 95% confidence intervals were calculated using a Cox proportional hazards model with covariates of treatment, number of bronchodilators during run-in, and geographical region.
- The analysis was conducted using the intent-to-treat (ITT) population.

Results

Table 1. Baseline characteristics

Characteristic	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)	Total (N=2425)
Age, years, mean (SD)	64.6 (8.4)	64.9 (8.5)	64.4 (8.5)	64.6 (8.5)
Female, n (%)	319 (39)	327 (41)	342 (42)	988 (41)
Current smoker at screening, n (%)	394 (49)	396 (49)	413 (51)	1203 (50)
Smoking pack-years, mean (SD)	49.4 (27.7)	47.6 (25.9)	48.1 (25.8)	48.4 (26.5)
COPD duration, years, mean (SD)	8.8 (6.9)	7.8 (6.0)	8.3 (6.7)	8.3 (6.6)
Moderate COPD exacerbation history in prior year*, n (%)	123 (15)	124 (15)	146 (18)	393 (16)
Post-albuterol % predicted FEV_1, mean (SD)	54.9 (12.8)	55.9 (12.6)	55.6 (12.8)	55.4 (12.7)
% reversibility to albuterol, mean (SD)	10.4 (12.8)	10.2 (13.3)	10.7 (13.3)	10.5 (13.1)
Maintenance naïve, n (%)	250 (31)	250 (31)	249 (31)	749 (31)
Rescue albuterol, puffs/day, mean (SD)	2.2 (2.6)	2.1 (2.3)	2.2 (2.5)	2.2 (2.5)
Baseline CAT score, mean (SD)	19.1 (5.9)	19.3 (6.2)	19.3 (6.3)	19.2 (6.1)

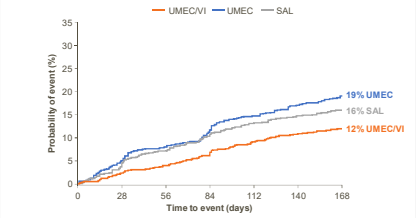
*Number of exacerbations requiring oral or systemic corticosteroids and/or antibiotics in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded).
CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second

Table 2. Study treatment withdrawal

	UMEC/VI (N=812)	UMEC (N=804)	SAL (N=809)	Total (N=2425)
Treatment status, n (%)				
Completed	716 (88)	651 (81)	683 (84)	2050 (85)
Discontinued	95 (12)	153 (19)	126 (16)	374 (15)
Unknown	1 (<1)	0	0	1 (<1)
Primary reason for study treatment withdrawal, n (%)				
Withdrawal by patient	33 (4)	57 (7)	49 (6)	139 (6)
Adverse event	27 (3)	30 (4)	22 (3)	79 (3)
Lack of efficacy	8 (<1)	16 (2)	16 (2)	40 (2)
Protocol withdrawal criteria met*	16 (2)	21 (3)	23 (3)	60 (2)
Lost to follow up	5 (<1)	14 (2)	2 (<1)	21 (<1)
Other†	6 (<1)	15 (2)	14 (2)	35 (1)

*Stopping criteria included: unstable or life-threatening cardiac event; two moderate or one severe COPD exacerbations; non-compliance with the study treatment or eDiary; †includes withdrawals due to protocol deviation, termination of the study, physician decision, and withdrawals with no known reason.

Figure 1. Kaplan–Meier curve for time to study treatment withdrawal



Number of patients at risk

UMEC/VI	812	794	781	764	740	727	460
UMEC	804	767	741	716	688	670	419
SAL	809	781	754	729	707	695	446

Figure 2. Risk reduction with UMEC/VI versus UMEC or SAL for each of the three endpoints

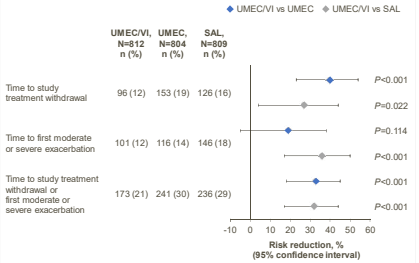
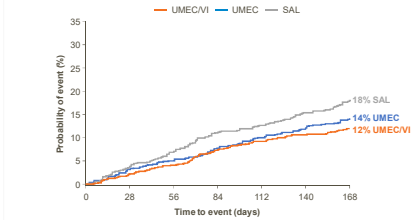


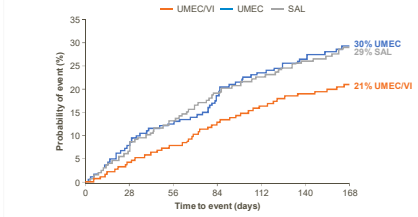
Figure 3. Kaplan–Meier curve for time to first on-treatment moderate/severe exacerbation



Number of patients at risk

UMEC/VI	812	779	749	711	681	660	421
UMEC	804	744	705	660	617	592	365
SAL	809	757	706	656	628	600	375

Figure 4. Kaplan–Meier curve for time to study treatment withdrawal or first on-treatment moderate/severe exacerbation



Number of patients at risk

UMEC/VI	812	777	749	711	680	660	421
UMEC	804	742	703	658	616	592	364
SAL	809	755	706	656	628	600	375

Baseline characteristics

- The ITT population included 2425 patients baseline characteristics were similar between treatment groups (**Table 1**).

Study treatment withdrawal

- The proportion of patients withdrawing was lower with UMEC/VI compared with either monotherapy in the ITT population (**Figure 1, Table 2**).
  - The risk of study treatment withdrawal was significantly lower with UMEC/VI versus UMEC (40% reduction) and SAL (27% reduction) (**Figure 2**).

Time to first moderate or severe exacerbation

- On treatment, a moderate or severe exacerbation was experienced by a smaller proportion of patients receiving UMEC/VI compared with UMEC or SAL in the ITT population (**Figure 3**).
  - The risk of an on-treatment moderate/severe exacerbation was significantly reduced with UMEC/VI versus SAL by 36%, but not UMEC (19% reduction) (**Figure 2**).
- Interestingly, the reduction in risk of study treatment withdrawal was greater for UMEC/VI versus UMEC compared with UMEC/VI versus SAL, whereas the reduction in risk of exacerbation was greater for UMEC/VI versus SAL.

Composite time to first study treatment withdrawal or first moderate/severe exacerbation

- A smaller proportion of patients receiving UMEC/VI withdrew from study treatment or had a moderate/severe exacerbation compared with UMEC or SAL in the ITT population (**Figure 4**).
  - The risk of a composite endpoint event was significantly reduced with UMEC/VI versus both UMEC (33% reduction) and SAL (32% reduction) (**Figure 2**).

Conclusions

- Significant differences between treatment groups in study treatment withdrawal may indicate sub-optimal responses to therapy among patients receiving monotherapy.
- A combined composite endpoint of exacerbation and study treatment withdrawal may better capture overall treatment failure in patients with symptomatic COPD than the individual endpoints alone.

References

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Disclosures

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