# Supplementary materials

**Supplementary Methods**

*Randomization*

Randomization was stratified by maintenance bronchodilator use during the run-in period (0 or 1 long-acting bronchodilator per day).

*Statistical analyses*

For the MMRM analysis of the primary endpoint, the model included covariates of baseline FEV1, geographical region, visit, treatment, visit by baseline FEV1 and visit by treatment interactions, where visit is nominal. For the responder analyses of the primary endpoint, the generalized linear mixed model included treatment as an explanatory variable and covariates of visit, baseline trough FEV1, geographical region, visit by baseline FEV1 and visit by treatment interactions. Unless stated otherwise, other efficacy endpoints were analyzed in a similar manner using the relevant baseline values for outcomes; for analyses of E-RS score and rescue medication use, the 4‑weekly period was included as a covariate instead of visit.

Time to first exacerbation HRs and 95% CIs were based on Cox proportional hazards model with covariates of treatment and geographical region. Time to first CID HRs and 95% CIs were based on a Cox proportional hazards model with covariates of treatment, geographical region, trough FEV1 at baseline, and SGRQ score at baseline.

For the post hoc analysis of an interaction between change from baseline in trough FEV1 and maintenance therapy status, the MMRM model included covariates of baseline FEV1, geographical region, number of bronchodilators received during run-in (0 or 1), visit, treatment, MN status, visit by baseline FEV1, visit by treatment, visit by MN status, treatment by MN status, and visit by treatment by MN status interactions (where visit is nominal). The interaction test for SAC-TDI focal score was conducted in a similar manner, with SAC-baseline dyspnea index score as the baseline value.

**Supplementary Table S1** IEC/IRB committees that approved the EMAX trial

|  |
| --- |
| Comité de Ética en Investigación. INAER, Arenales 3146 1° B, Ciudad Autónoma de Buenos Aires, C1425BEN, Argentina |
| CEICI, Italia 424, Rosario, Santa Fe, 2000, Argentina |
| CEMER, Esmeralda 1550, Florida, Buenos Aires, 1602, Argentina |
| CECIC Comité de Ética de CER Investigaciones Clínicas, Vicente Lopez 1441, Quilmes, Buenos Aires, 1878, Argentina |
| Comite Independiente de etica Fundacion Rusculleda, Avenida Colon 2057, Cordoba, Córdova, X5003DCE, Argentina |
| Framingham Centro Médico, Calle 9 Numero 431, La Plata, Buenos Aires, B1902COS, Argentina |
| Comité Independiente de ética para ensayos en Farmacología Clinica del centro Medico Dra. De Salvo, Avenida Cabildo 1536 5° B, Ciudad Autonoma de Buenos Aires, Buenos Aires, C1426ABP, Argentina |
| Instituto Argentino de Investigacion Neurologica, Uruguay 824 1st floor, Ciudad Autonoma de Buenis Aires, C1015ABR, Argentina |
| FUMELIT, Av. Gdor. Freyre 3074, Santa Fe, 3000, Argentina |
| CIDEA, 3er Cuerpo - 2do Subsuelo, Paraguay 2035, Ciudad Autónoma de Buenos Aires, C1121ABE, Argentina |
| Comite de Etica de San Isidro-CESI, Avenue Libertador 169581, San Isidro, Buenos Aires, CP 1643, Argentina |
| Comite de etica para la investigación Clinica Fundación Dr. J.R. Villavicencio, Alvear 854, Rosario, Santa Fe, 2000QGB, Argentina |
| Comite de Etica Iniciativa y Refelexion Bioetica Rosario, Rioja 2926, Rosario, S2002OJN, Argentina |
| CESIM, Urquiza 646, Santa Rosa, 6300, Argentina |
| Instituto de Investigacion Clinica de Mar del Plata, Av. Colon 3364 PB, Mar del Plata, Buenos Aires, B7600FZN, Argentina |
| Centro de Osteopatias Medicas, Azcuenaga 1860, Buenos Aires, C1128AAF, Argentina |
| Comite de Etica en Investigacion Clinica - CEIC, Larrea 1381, Ciudad Autonoma de Buenos Aires, Buenos Aires, C1117ABK, Argentina |
| Comite de Etica en Investigacion, Instituto Ave Pulmo, Carlos M. Alvear 3345, Mar del Plata,Buenos Aires, B7602DCK, Argentina |
| Bellberry Limited, 129 Glen Osmond Rd, Eastwood, South Australia, 5063, Australia |
| INSTITUTIONAL REVIEW BOARD Services, Suite 300, 372 Hollandview Trail, Aurora, Ontario, L4G 0A5, Canada |
| Comité d'éthique de la recherche de l'Institut universitaire de cardiologie et de pneumologie de Qué, 2725 Chemin Ste-Foy, Quebec, G1V 4G5, Canada |
| CHU Pontachaillou, Comité de Protection des Personnes, 9 Avenue de la Bataille Flandres-Dunkerque Mai 1940, Rennes, 35000, France |
| Ethik-Kommission der Landesaerztekammer Hessen, Im Vogelsgesang 3, Frankfurt, Hessen, 60488, Germany |
| Comitato Etico IRCCS Istituto Tumori "G.Paolo II", V.le Orazio Flacco 65, Bari, Puglia, 70124, Italy |
| Comitato Etico Campania Nord c/o A.O. San Giuseppe Moscati di Avellino, Segreteria Scientifico- Amministrativa, Città Ospedaliera -Pal. Uffici, Contrada Amoretta, Avellino, Campania, Italy |
| Com. Etico Reg. Toscano "Area Vasta Nord Ovest", Segreteria Scientifico-Amministrativa -Azienda Ospedaliero-Universitaria Pisana, Via Roma, 67, Pisa, Toscana, 56126, Italy |
| Comitato Etico Palermo 1, c/o Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Segreteria Scientifico-Amministrativa, Via del Vespro 129, Palermo, Sicilia, 90127, Italy |
| Comitato Etico Univ. Studi Campania L.Vanvitelli – AOU L.Vanvitelli - AORN Osp. dei Colli, Sede AORN Ospedali dei Colli, Via Leonardo Bianchi snc, Napoli, Campania, 80131, Italy |
| C.E.ROM. Comitato Etico della Romagna, c/o Ist. Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRST - IRCCS Srl, Via Piero Maroncelli 40, Meldola (FC), Emilia-Romagna, 47014, Italy |
| Comitato Etico Unico Regionale del Friuli Venezia Giulia, Segreteria Tecnico-Scientifica c/o Dir. Scientifica, IRCCS CRO di Aviano, Via Gallini, 2, Aviano (PN), Friuli-Venezia-Giulia, 33081, Italy |
| Comitato Etico dell'Area Vasta Emilia Nord, Via Vertoiba, 10A, Reggio Emilia, Emilia-Romagna,42124, Italy |
| Comitato Etico Aziende Sanitarie dell'Umbria, Segreteria Scientifico-Amministrativa, Via della Rivoluzione, 16, Ellera di Corciano (PG), Umbria, 6070, Italy |
| Comitato Etico Area 4 – ASL Brindisi, Segreteria Scientificoamministrativa, Via Napoli, 8, Brindisi, Puglia, 72100, Italy |
| Comitato Etico Univ. Studi Campania L.Vanvitelli – AOU L.Vanvitelli - AORN Osp. dei Colli, Sede AORN Ospedali dei Colli, Via Leonardo Bianchi snc, Napoli, Campania, 80131, Italy |
| Comitato Etico degli Istituti Clinici Scientifici Maugeri SpA – SB, Via Salvatore Maugeri 4, Pavia, Lombardia, 27100, Italy |
| Comitato Etico Campania Sud c/o ASL Napoli 3 Sud, Segreteria Scientifico-Amministrativa, Piazza San Giovanni, 7, Brusciano (NA), Campania, 80031, Italy |
| Hospital Real San Jose, Av Lázaro Cárdenas 4149 Colonia Jardines de San Ignacio, Zapopan, Jalisco, 45040, Mexico |
| Instituto Jalisciense de Investigación Clínica, S.A. de C.V., Penitenciaria 20, Guadalajara, Jalisco, 44100, Mexico |
| St. Antonius Ziekenhuis, Koekoekslaan 1, NIEUWEGEIN, 3435 CM, Netherlands |
| Pharma Ethics, 123 Amcor Road, Lyttelton Manor, 157, South Africa |
| University of Cape Town, Human Research Ethics Committee, Room E52.24, Old Main Building, Groote Schuur Hospital, Main Road, Observatory, 7925, South Africa |
| Fundació Unió Catalana d’Hospitals, 1ºA, C/Bruc 72-74, Barcelona, 8009, Spain |
| Regionala Etikprövningsnämnden I Göteborg, Guldhedsgatan 5A, GÖTEBORG, SE-413 20, Sweden |
| Advarra Institutional Review Board, Suite 110, 6940 Columbia Gateway Drive, Columbia, Maryland, 21046, United States |
| Saint Luke’s Hospital Institutional Review Board, 232 South Woods Mill Road, Chesterfield, Missouri, 63017, United States |
| South Carolina Pharmaceutical Research, 141 Harold Fleming Court, Spartanburg, South Carolina, 29303, United States |

**Supplementary Table S2** Baseline demographics and clinical characteristics by treatment arm

|  |  |  |
| --- | --- | --- |
|  | **MN****(N=749)** | **MT****(N=1676)** |
|  | **UMEC/VI****N=250** | **UMEC****N=250** | **SAL****N=249** | **UMEC/VI****N=562** | **UMEC****N=554** | **SAL****N=560** |
| **Age, years, mean (SD)** | 63.3 (8.0) | 63.4 (8.2) | 62.2 (8.8) | 65.2 (8.5) | 65.5 (8.5) | 65.3 (8.2) |
| **Female, n (%)** | 112 (45) | 121 (48) | 110 (44) | 207 (37) | 206 (37) | 232 (41) |
| **Current smoker, n (%)** | 161 (64) | 169 (68) | 163 (65) | 233 (41) | 227 (41) | 250 (45) |
| **Smoking pack-years, mean (SD)** | 53.2 (25.9) | 46.6 (24.1) | 49.8 (25.3) | 47.7 (28.4) | 48.1 (26.7) | 47.3 (26.0) |
| **Duration of COPD, years, mean (SD)** | 8.7 (7.4) | 7.8 (5.9) | 8.4 (6.9) | 8.8 (6.8) | 7.8 (6.0) | 8.2 (6.6) |
| **Moderate COPD exacerbation in past 12 monthsa, n (%)** | 27 (11) | 24 (10) | 26 (10) | 96 (17) | 100 (18) | 120 (21) |
| **Post-albuterol percent predicted FEV1, mean (SD)** | 57.7 (12.1) | 57.7 (12.0) | 55.7 (12.6) | 53.6 (12.9) | 55.1 (12.8) | 55.5 (12.9) |
| **Post-albuterol FEV1/FVC, mean (SD)** | 0.55 (0.09) | 0.54 (0.09) | 0.53 (0.10) | 0.50 (0.11) | 0.51 (0.10) | 0.51 (0.10) |
| **Percent reversibility to albuterol, mean (SD)** | 12.6 (13.2) | 13.0 (13.4) | 12.9 (12.0) | 9.4 (12.6) | 8.9 (13.0) | 9.8 (13.7) |
| **GOLD grade**b**, n (%)** |  |  |  |  |  |  |
| **2** | 187 (75) | 177 (71) | 162 (65) | 331 (59) | 352 (64) | 360 (64) |
| **3** | 63 (25) | 72 (29) | 87 (35) | 231 (41) | 199 (36) | 199 (36) |
| **Baseline FEV1, mL, mean (SD)** | 1559 (511) | 1528 (513) | 1536 (569) | 1436 (509) | 1491 (501) | 1477 (516) |
| **BDI focal score, mean (SD)** | 7.2 (2.0) | 7.1 (2.1) | 7.1 (2.0) | 6.9 (1.8) | 7.0 (1.9) | 7.0 (1.8) |
| **E-RS total score, mean (SD)** | 11.4 (5.7) | 11.9 (6.4) | 11.5 (6.0) | 10.4 (5.6) | 10.2 (5.5) | 9.9 (5.5) |
| **SGRQ score, mean (SD)** | 47.2 (16.5) | 48.1 (17.8) | 49.0 (17.1) | 43.3 (15.8) | 43.7 (15.1) | 42.6 (15.6) |
| **CAT score, mean (SD)** | 20.7 (6.2) | 21.4 (6.7) | 21.2 (6.7) | 18.4 (5.6) | 18.3 (5.7) | 18.4 (5.9) |
| **Rescue medication usec, puffs/day, mean (SD)** | 2.8 (3.1) | 2.7 (2.8) | 2.9 (3.0) | 1.9 (2.2) | 1.9 (2.1) | 1.8 (2.1) |
| **Rescue-free daysc, % (SD)** | 35.7 (41.4) | 37.9 (42.5) | 33.2 (40.4) | 40.5 (42.1) | 41.0 (41.3) | 41.6 (41.5) |

aNumber of patients with an exacerbation requiring oral or systemic corticosteroids and/or antibiotics (moderate) in 12 months prior to screening (patients with >1 moderate exacerbation or with a severe exacerbation [requiring hospitalization] were excluded from the study); ban additional 4 (<1%) patients with GOLD grade 1 (MN n=1; MT n=3) were randomized; cduring the 4-week run-in period.

BDI, Baseline Dyspnea Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms–COPD; FEV1; forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ITT, intent-to-treat;
MN, maintenance-naïve; MT, maintenance-treated; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire.

**Supplementary Table S3** Change from baseline in lung function and symptoms outcomes with UMEC versus SAL in MN and MT patients

|  |  |  |
| --- | --- | --- |
|  | **MN** | **MT** |
|  | **UMEC (N=250)** | **SAL (N=249)** | **UMEC (N=554)** | **SAL (N=560)** |
| **Lung function outcomes** |
| *Trough FEV1 at Week 24, mL* |  |  |  |  |
| LS mean CFB (95% CI) | 150 (120, 181) | 66 (36, 97) | 12 (-8, 32) | -56 (-75, -37) |
| UMEC vs SAL mean difference (95% CI) | **-** | **84 (41, 127)*****P*<0.001** | **-** | **68 (40, 95)*****P*<0.001** |
| *Trough FVC at Week 24, mL* |  |  |  |  |
| LS mean CFB (95% CI) | 161 (114, 209) | 66 (19, 114) | -8 (-40, 24) | -120 (-151, -89) |
| UMEC vs SAL mean difference (95% CI) | **-** | **95 (28, 162)*****P*=0.006** | **-** | **112 (68, 157)*****P*<0.001** |
| *Trough IC at Week 24, mL* |  |  |  |  |
| LS mean CFB (95% CI) | 127 (80, 174) | 85 (38, 131) | 39 (7, 70) | -50 (-81, -20) |
| UMEC vs SAL mean difference (95% CI) | **-** | 42 (-23, 108)*P*=0.207 | **-** | **89 (45, 133)*****P*<0.001** |
| **Symptom outcomes/severity changes** |
| *SAC-TDI focal score at Week 24* |  |  |  |  |
| LS mean CFB (95% CI) | 1.65 (1.24, 2.07) | 1.55 (1.14, 1.96) | 1.13 (0.87, 1.39) | 1.08 (0.83, 1.34) |
| UMEC vs SAL mean difference (95% CI) |  | 0.10 (-0.48, 0.69)*P*=0.735 |  | 0.05 (-0.32, 0.41)*P*=0.808 |
| *E-RS total score at Weeks 21–24* |  |  |  |  |
| LS mean CFB (95% CI) | -2.02 (-2.58, -1.46) | -1.70 (-2.25, -1.14) | -0.52 (-0.88, -0.17) | -0.24 (-0.59, 0.11) |
| UMEC vs SAL mean difference (95% CI) |  | -0.32 (-1.11, 0.46)*P*=0.421 |  | -0.28 (-0.78, 0.21)*P*=0.265 |
| *Rescue medication use over Weeks 1–24* |  |  |  |  |
| Mean inhalations/day |  |  |  |  |
| LS mean CFB (95% CI) | -0.82 (-1.02, -0.62) | -0.89 (-1.09, -0.69) | -0.03 (-0.15, 0.09) | -0.06 (-0.18, 0.05) |
| UMEC vs SAL mean difference (95% CI) | **-** | 0.07 (-0.22, 0.35)*P*=0.634 | **-** | 0.03 (-0.13, 0.20)*P*=0.686 |
| % rescue medication-free days |  |  |  |  |
| LS mean CFB (95% CI) | 11.3 (7.2, 15.3) | 13.6 (9.5, 17.6) | 4.5 (2.0, 6.9) | 5.0 (2.5, 7.4) |
| UMEC vs SAL mean difference (95% CI) | **-** | -2.3 (-8.0, 3.4)*P*=0.425 | **-** | -0.5 (-4.0, 3.0)*P*=0.772 |
| *GADS*a *at Week 24* |  |  |  |  |
| Proportion of patients reporting improvement from baseline at Week 24, n/N (%) | 128/196 (65) | 129/206 (63) | 265/442 (60) | 284/468 (61) |
| UMEC vs SAL ordered odds ratio for improvement in response category (95% CI) | **-** | 1.13 (0.80, 1.62)*P*=0.482 | **-** | 0.94 (0.74, 1.19)*P*=0.584 |

Bold text indicates statistically significant treatment differences with UMEC/VI versus UMEC or SAL. aOverall assessment of change in COPD severity was rated using a seven-point Likert scale (‘Much Better’, ‘Slightly Better’, ‘Better’, ‘No Change’, ‘Slightly Worse’, ‘Worse’, ‘Much Worse’); ordered response ratios were reported as odds of better response category;

CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms-COPD; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GADS, global assessment of disease severity; IC, inspiratory capacity; LS, least squares; MN, maintenance-naïve; MT, maintenance-treated; SAC-TDI, self-administered computerized Transition Dyspnea Index; SAL, salmeterol; UMEC, umeclidinium; VI, vilanterol.

**Supplementary Figure S1** LS mean change from baseline in trough FEV1 at Week 4, SAC-TDI focal score at Week 4, rescue medication inhalations/day over Weeks 1–4, and SGRQ score at Week 4 with UMEC/VI, UMEC, and SAL in (**A**) MN and (**B**) MT patients



All values are LS mean (95% CI). Negative changes from baseline are not shown; change from baseline in in trough FEV1 at Week 4 of -21 mL with SAL in the MT subgroup is presented as zero.

\**P*<0.05 vs UMEC and †vs SAL;

CI, confidence interval; FEV1, forced expiratory volume in 1 second; LS, least squares; MN, maintenance-naïve; MT, maintenance-treated; SAC-TDI, self-administered computerized Transition Dyspnea Index; SAL, salmeterol; SGRQ, St George’s Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

**Supplementary Figure S2** LS mean trough FEV1 at Week 24, SAC-TDI focal score at Week 24, rescue medication inhalations/day over Weeks 1–24, and SGRQ score at Week 24 with UMEC/VI, UMEC, and SAL in (**A**) MN and (**B**) MT patients



All values are LS mean (95% CI).

CI, confidence interval; FEV1, forced expiratory volume in 1 second; LS, least squares; MN, maintenance-naïve; MT, maintenance-treated; SAC-TDI, self-administered computerized Transition Dyspnea Index; SAL, salmeterol; SGRQ, St George’s Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.