## Supplementary Tables

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

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| 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, USA |
| Saint Luke’s Hospital Institutional Review Board, 232 South Woods Mill Road, Chesterfield, Missouri, 63017, USA |
| South Carolina Pharmaceutical Research, 141 Harold Fleming Court, Spartanburg, South Carolina, 29303, USA |

**Supplementary Table S2.** Patient demographics and baseline characteristics by smoking status and treatment

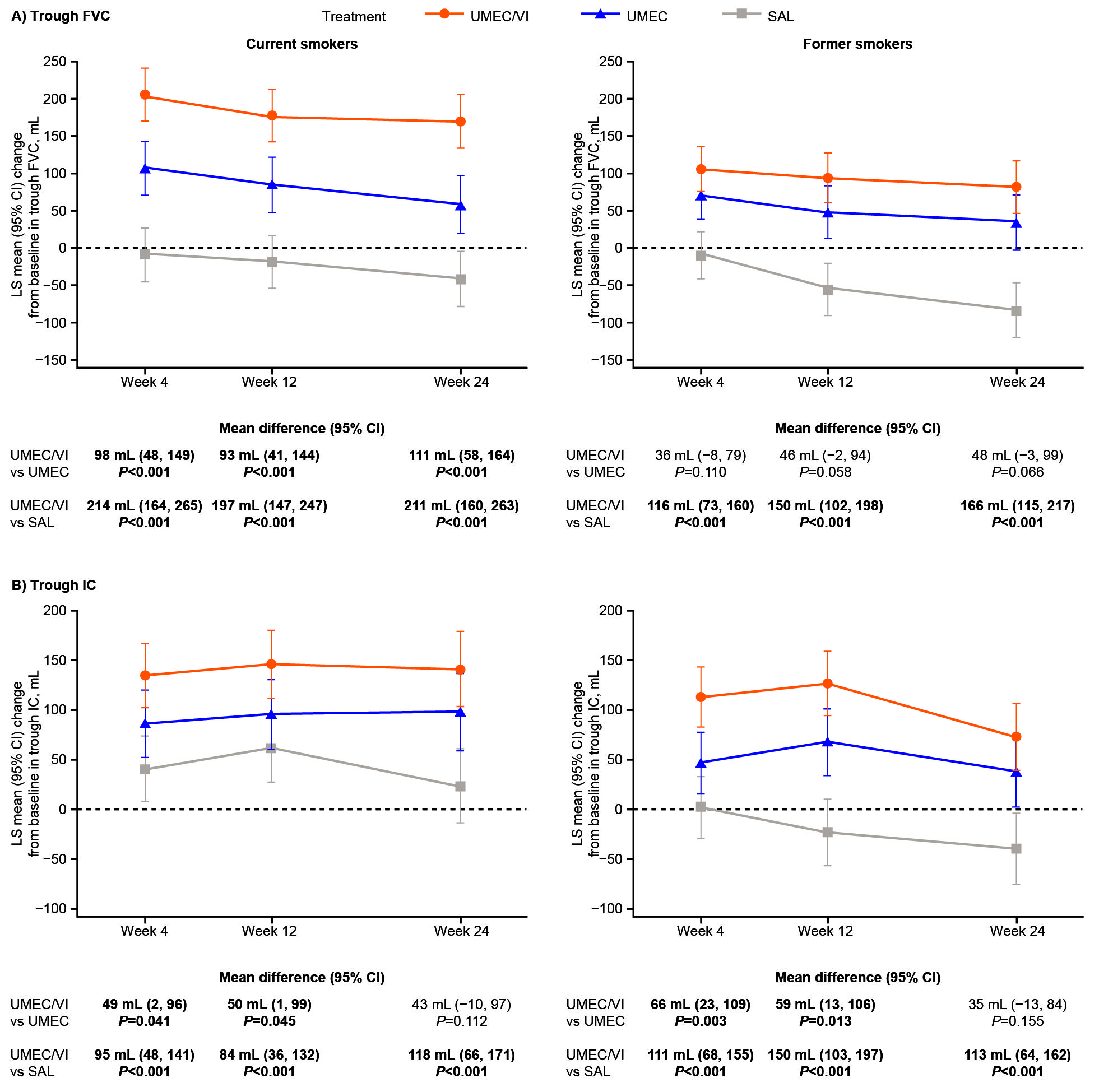
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| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Current smokers (N=1203)** | | | **Former smokers (N=1221)** | | |
| **UMEC/VI (n=394)** | **UMEC  (n=396)** | **SAL  (n=413)** | **UMEC/VI (n=418)** | **UMEC  (n=407)** | **SAL  (n=396)** |
| Age, years, mean (SD) | 61.9 (7.4) | 62.0 (7.7) | 61.3 (8.0) | 67.2 (8.4) | 67.7 (8.3) | 67.5 (7.9) |
| Female, n (%) | 180 (46) | 180 (45) | 201 (49) | 139 (33) | 147 (36) | 141 (36) |
| Smoking pack-years, mean (SD) | 50.6 (28.6) | 46.0 (22.7) | 47.5 (24.6) | 48.3 (26.9) | 49.3 (28.7) | 48.8 (27.0) |
| No prior maintenance medication (from 30 days prior to Screening) , n (%) | 161 (41) | 169 (43) | 163 (39) | 89 (21) | 80 (20) | 86 (22) |
| Patients with a moderate COPD exacerbation history in prior yeara, n (%) | 46 (12) | 55 (14) | 63 (15) | 77 (18) | 68 (17) | 83 (21) |
| Duration of COPD, years, mean (SD) | 8.3 (7.2) | 7.3 (5.8) | 7.6 (5.8) | 9.2 (6.7) | 8.3 (6.1) | 9.0 (7.5) |
| Post-salbutamol FEV1, mL, mean (SD) | 1635 (512) | 1653 (493) | 1652 (539) | 1523 (495) | 1567 (511) | 1545 (500) |
| Post-salbutamol % predicted FEV1, mean (SD) | 55.7 (12.6) | 56.3 (12.4) | 56.0 (12.6) | 54.1 (12.9) | 55.5 (12.9) | 55.2 (13.0) |
| Post-salbutamol FEV1/FVC, mean (SD) | 0.52 (0.11) | 0.53 (0.10) | 0.52 (0.09) | 0.51 (0.10) | 0.52 (0.10) | 0.51 (0.10) |
| % reversibility to salbutamol, mean (SD) | 10.2 (11.4) | 11.2 (13.3) | 11.0 (12.6) | 10.7 (14.1) | 9.2 (13.2) | 10.5 (13.9) |
| GOLD spirometric gradeb, n (%) |  |  |  |  |  |  |
| 2 | 260 (66) | 269 (68) | 267 (65) | 258 (62) | 260 (64) | 255 (64) |
| 3 | 134 (34) | 124 (31) | 145 (35) | 160 (38) | 146 (36) | 141 (36) |
| FEV1, mL, mean (SD) | 1527 (511) | 1553 (485) | 1554 (546) | 1423 (509) | 1454 (520) | 1434 (513) |
| BDI score, mean (SD) | 7.0 (1.9) | 7.0 (2.1) | 7.1 (1.9) | 7.0 (1.8) | 7.0 (1.8) | 7.1 (1.8) |
| E-RS total score | 11.5 (5.5) | 11.7 (6.0) | 11.2 (5.8) | 9.9 (5.7) | 9.8 (5.6) | 9.5 (5.4) |
| SGRQ score, mean (SD) | 45.6 (16.1) | 47.4 (17.3) | 46.7 (17.1) | 43.4 (16.1) | 42.7 (14.5) | 42.3 (15.1) |
| CAT score, mean (SD) | 19.9 (6.2) | 20.4 (6.5) | 20.4 (6.6) | 18.3 (5.5) | 18.2 (5.7) | 18.1 (5.8) |
| Rescue salbutamol, puffs/day, mean (SD) | 2.4 (2.8) | 2.5 (2.6) | 2.5 (2.6) | 2.0 (2.2) | 1.8 (2.0) | 1.8 (2.3) |

aNumber of exacerbations 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);ban additional 4 (<1%) current smokers with GOLD grade 1 were randomized (UMEC n=3; SAL n=1).

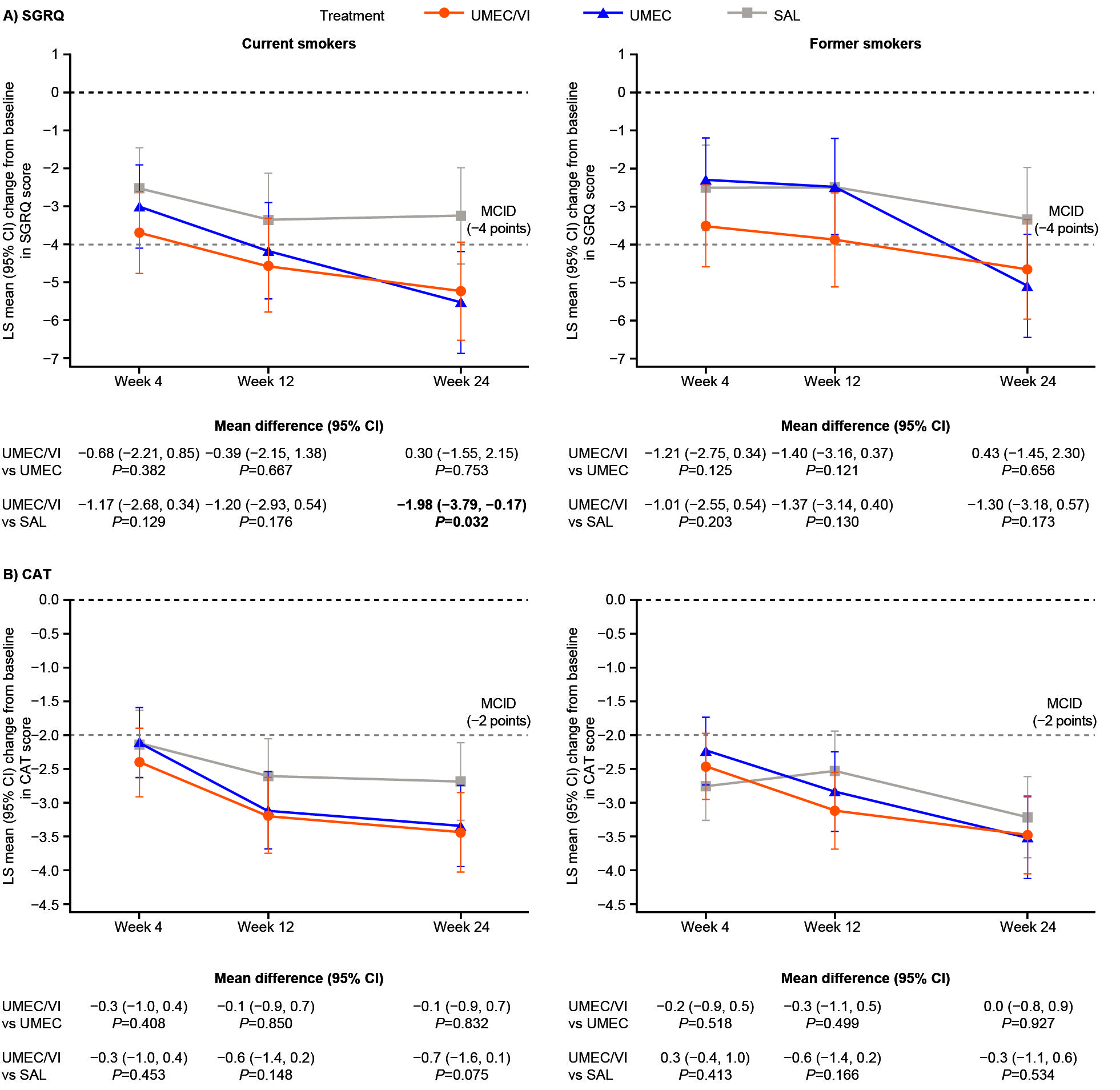
BDI, Baseline Dyspnoea Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; E-RS, Evaluating Respiratory Symptoms–COPD; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SAL, salmeterol; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

## Supplementary Figure Legends

**Supplementary Figure S1.** Change from baseline in (**A**) trough FVC and (**B**) trough IC at Weeks 4, 12, and 24 in current smokers and former smokers



CI, confidence interval; FVC, forced vital capacity; IC, inspiratory capacity; LS, least squares; SAL, salmeterol; UMEC, umeclidinium; VI, vilanterol.



**Supplementary Figure S2.** Change from baseline in (**A**) SGRQ score and (**B**) CAT score at Weeks 4, 12, and 24 in current smokers and former smokers

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CI, confidence interval; LS, least squares; MCID, minimum clinically important difference; SAL, salmeterol; SGRQ, St George’s Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.