Supplementary Material

Adherence and persistence with single-inhaler triple therapy among patients with COPD using commercial and Medicare Advantage US health plan claims data

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Table S1 Variables included in the propensity score model

Variables[a]
Demographic characteristics *(assessed on index date)* • Age • Sex • US geographic region • Insurance plan type (i.e., PPO, HMO, POS, and other types) • Insurance pay type (i.e., Commercial, Medicare Advantage, and Medicaid) • Year and month of index date • Physician specialty closest to the index date
Clinical characteristics *(assessed during the baseline period [or index date when indicated])* • COPD-related exacerbations – COPD-related exacerbations (i.e., number of exacerbations and proportion with ≥1 exacerbation) were assessed during the baseline period and, separately, on the index date: – Severe COPD-related exacerbations were defined as a hospitalization with a COPD exacerbation diagnosis code in the primary position – Moderate COPD-related exacerbations were defined as an OP or ED visit with a COPD exacerbation diagnosis code in the primary position and ≥1 dispensing or administration for a SCS or guideline-recommended antibiotic within 5 days following, or prior to, the visit – Of note, index exacerbations were considered as part of the baseline period and not included in the outcome measures • Other clinical characteristics – Quan-CCI [1] – Elixhauser comorbidities (those with ≥10% prevalence in either cohort) – Respiratory medication use (those with ≥5% use): – Maintenance medications: ○ ICS ○ LABA ○ LAMA ○ ICS/LABA ○ LAMA/LABA ○ Methylxanthines ○ Leukotriene modifiers ○ Biologics – Rescue medications: ○ SABA ○ SAMA ○ SABA/SAMA ○ SCS – Other therapies: ○ Antibiotics

- Maintenance medication used leading up to triple therapy initiation (classes and agents with ≥5% use):
    - Defined as the most recent maintenance medication used immediately before SITT initiation at the class and agent level
- All-cause and COPD-related HRU
    - COPD-related HRU was identified as any claim with a primary or secondary diagnosis of COPD
    - Number of visits during the baseline period and proportion of patients with ≥1 visit during the baseline period and on the index date were reported separately
    - For each type of HRU, the following endpoints were evaluated:
        - IP visits (i.e., hospitalizations)
        - ED visits
        - OP visits
        - Other visits
- All-cause and COPD-related costs
    - All-cause and COPD-related healthcare costs (COPD-related costs identified as any claim with a primary or secondary diagnosis of COPD) were computed as the health plan paid amounts during the baseline period. Costs were inflation-adjusted to the most recent year in US dollars based on the medical care component of the Consumer Price Index. The following costs were calculated:
        - Total costs (i.e., medical and pharmacy costs)
            - Total medical costs, which is the sum of the following individual cost components:
                - IP visit costs
                - ED visit costs
                - OP visit costs
                - Other visit costs
            - Pharmacy costs (only for all-cause costs)
        - SITT pharmacy costs

[a]Patients receiving FF/UMEC/VI and BUD/GLY/FOR were weighted using the inverse probability of treatment weighting approach based on the propensity score. Variables used in the propensity score calculation included the following: age, sex, year/quarter of index date, physician specialty, US region, type of insurance plan (i.e., PPO, HMO, POS, and other types), type of insurance pay (i.e., commercial, Medicare Advantage, and Medicaid), Quan-CCI score, presence of moderate and severe COPD-related exacerbations at baseline, presence of exacerbation on the index date, respiratory medication use (those with ≥5% use), controller medication used leading up to triple therapy initiation (classes and agents with ≥5% use), COPD-related HRU and medical costs (hospitalization, ER, and OP components), SITT pharmacy costs on the index date, and comorbidities (those with ≥10% prevalence in either cohort).

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CCI* Charlson comorbidity index, *COPD* chronic obstructive pulmonary disease, *ED* emergency department,

FF/UMEC/VI fluticasone furoate/umeclidinium/vilanterol, *HMO* health maintenance organization, *HRU* healthcare resource utilization, *ICS* inhaled corticosteroid, *IP* inpatient, *LABA* long-acting β2 agonist, *LAMA* long-acting muscarinic antagonist, *OP* outpatient, *POS* point-of-service, *PPO* preferred provider organization, *SABA* short-acting β2 agonist, *SAMA* short-acting muscarinic antagonist, *SCS* systemic corticosteroid, *SITT* single-inhaler triple therapy

Table S2 Unweighted and weighted patient baseline demographics and clinical characteristics

Characteristics (evaluated in the 12 months prior to treatment initiation)	**Unweighted cohorts**			**Weighted cohorts**		
	FF/UMEC/VI cohort (*n* = 8912)	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a,b], %**	**FF/UMEC/VI cohort (*n* = 8912)**	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a,b], %**
Follow-up period duration, days, mean (SD)	327.21 (57.37)	314.10 (61.19)	22.1	324.51 (58.30)	320.45 (60.31)	6.8
Demographics[c]						
Age, years, mean (SD)	65.05 (9.22)	63.19 (8.41)	21.1	64.62 (9.14)	63.96 (8.77)	7.3
Age, years, *n* (%)						
40–49	335 (3.8)	128 (4.8)	5.0	356 (4.0)	115 (4.3)	1.5
50–59	2280 (25.6)	831 (30.9)	11.9	2411 (27.1)	769 (28.6)	3.6
60–64	2652 (29.8)	876 (32.6)	6.2	2719 (30.5)	840 (31.3)	1.7
≥65	3645 (40.9)	850 (31.7)	19.3	3426 (38.4)	961 (35.8)	5.5
Female, *n* (%)	4594 (51.5)	1374 (51.2)	0.8	4590 (51.5)	1387 (51.7)	0.3
Region, *n* (%)						
South	4027 (45.2)	1391 (51.8)	13.3	4191 (47.0)	1316 (49.0)	4.0
Midwest	3407 (38.2)	930 (34.6)	7.5	3313 (37.2)	950 (35.4)	3.7
West	529 (5.9)	115 (4.3)	7.5	496 (5.6)	149 (5.5)	0.1
Northeast	928 (10.4)	242 (9.0)	4.7	894 (10.0)	261 (9.7)	1.0
Year of index date, *n* (%)						
2020	1039 (11.7)	105 (3.9)	29.2	876 (9.8)	243 (9.1)	2.6
Q4	1039 (11.7)	105 (3.9)	29.2	876 (9.8)	243 (9.1)	2.6

2021	4548 (51.0)	1161 (43.2)	15.7	4362 (48.9)	1262 (47.0)	3.9
Q1	1293 (14.5)	257 (9.6)	15.2	1184 (13.3)	341 (12.7)	1.8
Q2	1255 (14.1)	345 (12.8)	3.6	1219 (13.7)	340 (12.7)	3.0
Q3	1036 (11.6)	289 (10.8)	2.7	1013 (11.4)	302 (11.2)	0.4
Q4	964 (10.8)	270 (10.1)	2.5	946 (10.6)	280 (10.4)	0.6
2022	3325 (37.3)	1419 (52.8)	31.6	3674 (41.2)	1180 (43.9)	5.5
Q1	1182 (13.3)	375 (14.0)	2.1	1202 (13.5)	387 (14.4)	2.7
Q2	1138 (12.8)	604 (22.5)	25.7	1357 (15.2)	429 (16.0)	2.0
Q3	992 (11.1)	428 (15.9)	14.1	1096 (12.3)	358 (13.3)	3.1
Q4	13 (0.1)	12 (0.4)	5.5	19 (0.2)	6 (0.2)	0.2
Insurance plan type[c], *n* (%)						
PPO	4837 (54.3)	1545 (57.5)	6.6	4938 (55.4)	1580 (58.8)	6.9
HMO	3517 (39.5)	951 (35.4)	8.4	3404 (38.2)	933 (34.7)	7.2
POS	404 (4.5)	140 (5.2)	3.2	411 (4.6)	133 (5.0)	1.7
Indemnity/traditional	25 (0.3)	4 (0.1)	2.8	27 (0.3)	3 (0.1)	3.7
CDHC	121 (1.4)	43 (1.6)	2.0	125 (1.4)	32 (1.2)	1.9
Unknown	8 (0.1)	2 (0.1)	0.5	7 (0.1)	3 (0.1)	1.6
Insurance pay type[c], *n* (%)						
Commercial	5088 (57.1)	1807 (67.3)	21.2	5332 (59.8)	1717 (63.9)	8.4
Medicare Advantage	3811 (42.8)	878 (32.7)	20.9	3567 (40.0)	968 (36.1)	8.1
Medicaid	13 (0.1)	0.0 (0.0)	5.4	13 (0.1)	0.0 (0.0)	5.4

Physician specialty closest to the index date[c], *n* (%)						
Primary care[d]	4145 (46.5)	1267 (47.2)	1.4	4176 (46.9)	1273 (47.4)	1.1
Respiratory specialist[e]	2229 (25.0)	624 (23.2)	4.1	2189 (24.6)	646 (24.1)	1.2
Allergist	24 (0.3)	8 (0.3)	0.5	25 (0.3)	11 (0.4)	2.4
Pulmonologist	2206 (24.8)	616 (22.9)	4.3	2165 (24.3)	635 (23.6)	1.5
Other	1978 (22.2)	606 (22.6)	0.9	1979 (22.2)	607 (22.6)	0.9
Missing	560 (6.3)	188 (7.0)	2.9	567 (6.4)	160 (6.0)	1.7
Quan-CCI score[f] [1], mean (SD)	2.08 (1.60)	1.98 (1.53)	6.3	2.06 (1.59)	2.05 (1.60)	0.4
Quan-CCI score[f] [1], *n* (%)						
0–2	5951 (66.8)	1867 (69.5)	5.9	6009 (67.4)	1818 (67.7)	0.6
¾	2176 (24.4)	612 (22.8)	3.8	2139 (24.0)	634 (23.6)	0.9
≥5	785 (8.8)	206 (7.7)	4.1	763 (8.6)	233 (8.7)	0.4
All-cause HRU						
Patients with ≥1 visit during the baseline period excluding the index date[f], *n* (%)						
Hospitalization	1976 (22.2)	533 (19.9)	5.7	1932 (21.7)	585 (21.8)	0.3
ED visit	4024 (45.2)	1155 (43.0)	4.3	4031 (45.2)	1151 (42.9)	4.7
OP visit	8882 (99.7)	2678 (99.7)	1.4	8883 (99.7)	2678 (99.7)	1.4
Other visit	3924 (44.0)	1084 (40.4)	7.4	3891 (43.7)	1031 (38.4)	10.7
Number of HRU events during the baseline period excluding the index date[f], mean (SD)						

Hospitalization	0.31 (0.73)	0.27 (0.65)	5.7	0.30 (0.72)	0.32 (0.73)	1.5
ED visits	0.99 (1.70)	0.96 (1.81)	1.6	0.99 (1.70)	0.99 (1.88)	0.1
OP visits	19.04 (17.27)	19.28 (17.32)	1.4	19.23 (18.11)	19.10 (16.47)	0.8
Other visit	1.68 (7.07)	1.48 (6.56)	2.8	1.66 (7.06)	1.38 (5.44)	4.5
Patients with ≥1 visit on the index date[c], *n* (%)						
Hospitalization	130 (1.5)	10 (0.4)	11.4	115 (1.3)	20 (0.8)	5.3
ED visit	50 (0.6)	10 (0.4)	2.8	54 (0.6)	9 (0.3)	4.0
OP visit	4679 (52.5)	1053 (39.2)	26.9	4428 (49.7)	1232 (45.9)	7.6
Other visit	121 (1.4)	21 (0.8)	5.6	113 (1.3)	22 (0.8)	4.6
COPD-related HRU[g]						
Patients with ≥1 visit during the baseline period excluding the index date[f], *n* (%)						
Hospitalization	1716 (19.3)	454 (16.9)	6.1	1672 (18.8)	505 (18.8)	0.1
ED visit	2405 (27.0)	671 (25.0)	4.6	2380 (26.7)	664 (24.7)	4.5
OP visit	8617 (96.7)	2637 (98.2)	9.7	8634 (96.9)	2631 (98.0)	6.9
Other visit	1056 (11.8)	286 (10.7)	3.8	1035 (11.6)	277 (10.3)	4.2
Number of HRU events during the baseline period excluding the index date[f], mean (SD)						
Hospitalizations	0.26 (0.64)	0.22 (0.55)	6.2	0.25 (0.62)	0.26 (0.62)	1.4
ED visits	0.46 (1.03)	0.43 (1.01)	3.0	0.45 (1.02)	0.44 (1.08)	0.8

OP visits	4.74 (5.90)	5.11 (5.32)	6.5	4.93 (8.09)	4.96 (5.09)	0.4
Other visit	0.22 (1.37)	0.21 (1.26)	0.8	0.22 (1.39)	0.21 (1.10)	1.2
Patients with ≥1 visit on the index date[c], *n* (%)						
Hospitalization	128 (1.4)	10 (0.4)	11.3	113 (1.3)	20 (0.8)	5.1
ED visit	34 (0.4)	5 (0.2)	3.7	37 (0.4)	5 (0.2)	4.3
OP visit	4036 (45.3)	864 (32.2)	27.2	3744 (42.0)	1075 (40.0)	4.0
Other visit	80 (0.9)	13 (0.5)	5.0	72 (0.8)	14 (0.5)	3.5
All-cause healthcare costs[f,h], $US 2022, mean (SD)						
Total costs (medical + pharmacy)	23,509.28 (38,695.58)	23,386.40 (38,056.96)	0.3	23,540.31 (39,017.72)	23,710.01 (37,041.38)	0.5
Total medical costs	16,105.36 (34,251.67)	15,793.72 (34,312.00)	0.9	16,134.23 (34,581.51)	15,859.43 (33,096.78)	0.8
IP visit costs	7569.38 (28,410.50)	6906.35 (28,577.04)	2.3	7422.25 (28,715.76)	7448.93 (27,815.14)	0.1
ED visit costs	1438.63 (3896.41)	1506.14 (3902.01)	1.7	1467.29 (4092.65)	1485.97 (3702.80)	0.5
OP visit costs	7097.35 (13,722.44)	7381.23 (13,809.71)	2.1	7244.70 (13,856.73)	6924.54 (12,562.73)	2.4
Other visit costs	609.26 (2695.73)	681.06 (3793.93)	2.2	605.75 (2704.77)	595.04 (2891.05)	0.4
Pharmacy costs	7403.93 (15,331.17)	7592.68 (14,794.72)	1.3	7406.08 (15,493.81)	7850.58 (15,016.66)	2.9

COPD-related healthcare costs[f,g,h], $US 2022, mean (SD)						
Total medical costs	9419.58 (26,453.43)	9128.55 (25,826.89)	1.1	9403.78 (26,954.36)	9299.96 (24,634.20)	0.4
IP visit costs	6123.34 (24,764.13)	5469.87 (23,686.33)	2.7	5975.15 (25,199.05)	5948.01 (22,753.78)	0.1
ED visit costs	868.31 (3050.59)	886.44 (2814.37)	0.6	886.00 (3277.33)	875.36 (2692.38)	0.4
OP visit costs	2427.94 (6110.94)	2772.25 (7393.01)	5.1	2542.63 (6412.25)	2476.59 (6601.91)	1.0
Other visit costs	224.95 (1024.49)	270.86 (1381.05)	3.8	222.50 (1035.91)	255.77 (1261.20)	2.9

[a]For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs.

[b]For dichotomous variables, the standardized difference was calculated using the following equation where P is the respective proportion of participants in each group: $|(P^{case}-P^{control})| / \sqrt{[(P^{case}(1-P^{case})+P^{control}(1-P^{control}))/2]}$.

[c]Evaluated at the index date (i.e., the date of the first pharmacy claim for single-inhaler FF/UMEC/VI or BUD/GLY/FOR).

[d]Included family medicine practitioner, internal medicine, nurse practitioner, and physician assistant.

[e]Allergist and pulmonologist were not mutually exclusive categories as some patients may have had claims for both specialists on the same day.

[f]Evaluated during the 12-month baseline period, excluding the index date.

[g]COPD-related claims were identified as any claim with a primary or secondary diagnosis of COPD.

[h]Costs were inflated to $US 2022 using the U.S. Medical Care consumer price index from the Bureau of Labor Statistics from the U.S. Department of Labor.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CCI* Charlson comorbidity index, *CDHC* consumer-directed health care, *COPD* chronic obstructive pulmonary disease, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *HMO* health maintenance organization, *HRU* healthcare resource utilization, *IP* inpatient, *OCS* oral corticosteroid, *OP* outpatient, *POS* point-of-service, *PPO* preferred provider organization, *SCS* systemic corticosteroid, *SD* standard deviation.

Table S3 Baseline respiratory medication

Medications (evaluated in the 12 months prior to treatment initiation)	**Unweighted cohorts**			**Weighted cohorts**		
	FF/UMEC/VI cohort (*n* = 8912)	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a], %**	**FF/UMEC/VI cohort (*n* = 8912)**	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a,b], %**
Respiratory medication class[c], *n* (%)						
Maintenance medications						
ICS/LABA	3325 (37.3)	1219 (45.4)	16.5	3503 (39.3)	1081 (40.3)	2.0
LAMA/LABA	1910 (21.4)	399 (14.9)	17.1	1780 (20.0)	536 (20.0)	0.0
LAMA	1524 (17.1)	473 (17.6)	1.4	1528 (17.1)	463 (17.2)	0.3
Leukotriene modifiers	1172 (13.2)	444 (16.5)	9.5	1244 (14.0)	371 (13.8)	0.4
ICS	538 (6.0)	174 (6.5)	1.8	541 (6.1)	163 (6.1)	0.0
Methylxanthines	94 (1.1)	37 (1.4)	2.9	88 (1.0)	35 (1.3)	3.0
LABA	63 (0.7)	29 (1.1)	4.0	62 (0.7)	28 (1.0)	3.6
Biologic agents	16 (0.2)	1 (0.0)	4.3	18 (0.2)	1 (0.0)	4.8
Rescue medications						
SABA	6190 (69.5)	1917 (71.4)	4.3	6233 (69.9)	1871 (69.7)	0.5
SAMA/SABA	1670 (18.7)	564 (21.0)	5.7	1711 (19.2)	508 (18.9)	0.7
SAMA	187 (2.1)	61 (2.3)	1.2	188 (2.1)	50 (1.9)	1.7
Other therapies						
Antibiotics	5664 (63.6)	1830 (68.2)	9.7	5771 (64.8)	1764 (65.7)	2.0
Systemic corticosteroids	5585 (62.7)	1800 (67.0)	9.2	5690 (63.9)	1736 (64.7)	1.7

Maintenance medication used leading up to triple therapy initiation[d], *n* (%)						
ICS/LABA	2839 (31.9)	1029 (38.3)	13.6	2983 (33.5)	916 (34.1)	1.4
Budesonide/formoterol	1092 (12.3)	665 (24.8)	32.6	1362 (15.3)	422 (15.7)	1.2
Fluticasone/salmeterol	811 (9.1)	206 (7.7)	5.2	781 (8.8)	239 (8.9)	0.4
Fluticasone/vilanterol	801 (9.0)	111 (4.1)	19.7	699 (7.8)	216 (8.1)	0.8
Mometasone/formoterol	142 (1.6)	48 (1.8)	1.5	148 (1.7)	40 (1.5)	1.3
LAMA/LABA	1737 (19.5)	349 (13.0)	17.7	1608 (18.0)	482 (17.9)	0.3
Umeclidinium/vilanterol	1388 (15.6)	189 (7.0)	27.2	1212 (13.6)	360 (13.4)	0.6
Tiotropium/olodaterol	350 (3.9)	160 (6.0)	9.4	396 (4.4)	122 (4.5)	0.4
LAMA	1062 (11.9)	307 (11.4)	1.5	1047 (11.7)	329 (12.3)	1.6
Tiotropium	1062 (11.9)	307 (11.4)	1.5	1047 (11.7)	329 (12.3)	1.6
ICS	345 (3.9)	108 (4.0)	0.8	345 (3.9)	99 (3.7)	0.9
Fluticasone	158 (1.8)	32 (1.2)	4.8	150 (1.7)	28 (1.1)	5.4
Budesonide	140 (1.6)	61 (2.3)	5.1	148 (1.7)	54 (2.0)	2.7
Beclomethasone	37 (0.4)	11 (0.4)	0.1	38 (0.4)	12 (0.4)	0.4
Mometasone	10 (0.1)	4 (0.1)	1.0	10 (0.1)	5 (0.2)	1.6
LABA	41 (0.5)	17 (0.6)	2.3	42 (0.5)	15 (0.5)	1.1
Arformoterol	15 (0.2)	9 (0.3)	3.3	15 (0.2)	6 (0.2)	1.1
Salmeterol	15 (0.2)	1 (0.0)	4.1	15 (0.2)	1 (0.0)	4.8
Formoterol	11 (0.1)	7 (0.3)	3.1	12 (0.1)	8 (0.3)	3.7
No maintenance medication identified	3178 (35.7)	957 (35.6)	0.0	3165 (35.5)	932 (34.7)	1.7

[a]For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs.

[b]For dichotomous variables, the standardized difference was calculated using the following equation where P is the respective proportion of participants in each group: $|(P^{case}-P^{control})| / \sqrt{[(P^{case}(1-P^{case})+P^{control}(1-P^{control}))/2]}$.

[c]Evaluated during the 12-month baseline period, excluding the index date.

[d]Defined as the most recent maintenance medication used immediately before SITT initiation.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *ICS* inhaled corticosteroid, *LABA* long-acting β2 agonist, *LAMA* long-acting muscarinic antagonist, *SABA* short-acting β2 agonist, *SAMA* short-acting muscarinic antagonist, *SD* standard deviation, *SITT* single-inhaler triple therapy

Table S4 COPD-related exacerbations during the baseline period and on the index date

COPD-related exacerbations	Unweighted cohorts			Weighted cohorts		
	FF/UMEC/VI cohort (*n* = 8912)	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a,b], %**	**FF/UMEC/VI cohort (*n* = 8912)**	**BUD/GLY/FOR cohort (*n* = 2685)**	**Standardized differences[a,b], %**
Patients with ≥1 event during the baseline period excluding the index date[c], *n* (%)						
Any exacerbation[d]	1741 (19.5)	568 (21.2)	4.0	1785 (20.0)	582 (21.7)	4.1
Severe exacerbation[e]	1094 (12.3)	319 (11.9)	1.2	1078 (12.1)	344 (12.8)	2.2
Moderate exacerbation[f]	737 (8.3)	277 (10.3)	7.1	803 (9.0)	268 (10.0)	3.3
Number of events during the baseline period excluding the index date[c], mean (SD)						
Any exacerbation[d]	1.19 (0.74)	1.24 (0.67)	7.8	1.20 (0.73)	1.23 (0.68)	3.0
Severe exacerbation[e]	0.68 (0.71)	0.63 (0.65)	8.4	0.66 (0.70)	0.65 (0.67)	1.3
Moderate exacerbation[f]	0.51 (0.77)	0.62 (0.80)	14.2	0.54 (0.78)	0.57 (0.78)	3.8
Patients with ≥1 event on the index date[g], *n* (%)						
Any exacerbation[d]	208 (2.3)	28 (1.0)	10.0	182 (2.0)	65 (2.4)	2.6
Severe exacerbation[e]	117 (1.3)	7 (0.3)	11.9	102 (1.1)	17 (0.6)	5.2
Moderate exacerbation[f]	91 (1.0)	21 (0.8)	2.5	80 (0.9)	48 (1.8)	7.7

[a]For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs.

[b]For dichotomous variables, the standardized difference was calculated using the following equation where P is the respective proportion of participants in each group: $|(P^{case}-P^{control})| / \sqrt{[(P^{case}(1-P^{case})+P^{control}(1-P^{control}))/2]}$.

[c]The baseline period was defined as the 12 months prior to the index date.

[d]Any exacerbation included both moderate and severe COPD exacerbations.

[e]Severe exacerbations were defined as an IP hospitalization with a COPD exacerbation diagnosis code in the primary position.

[f]Moderate exacerbations were defined as an OP or ED visit with a COPD exacerbation diagnosis code in the primary position and at least one dispensing/administration of a systemic corticosteroid or guideline-recommended antibiotic within 5 days following, or prior to, the visit.

[g]Evaluated on the index date (i.e., the date of the first pharmacy claim for single-inhaler FF/UMEC/VI or BUD/GLY/FOR).

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *COPD* chronic obstructive pulmonary disease, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *IP* inpatient, *OP* outpatient, *SD* standard deviation

Table S5 Unweighted and weighted patient baseline demographics and clinical characteristics – minimum 12 months of follow-up (sensitivity analysis)

Characteristics (evaluated in the 12 months prior to treatment initiation)	**Unweighted cohorts**			**Weighted cohorts**		
	FF/UMEC/VI cohort (*n* = 5367)	**BUD/GLY/FOR cohort (*n* = 1268)**	**Standardized differences[a,b], %**	**FF/UMEC/VI cohort (*n* = 5367)**	**BUD/GLY/FOR cohort (*n* = 1268)**	**Standardized differences[a,b], %**
Follow-up period duration, days, mean (SD)	365.00 (0)	365.00 (0)	0.0	365.00 (0)	365.00 (0)	0.0
Demographics[c]						
Age, years, mean (SD)	65.01 (9.23)	62.01 (7.91)	35.0	64.44 (9.10)	63.87 (8.77)	6.4
Age, years, *n* (%)						
40–49	196 (3.7)	65 (5.1)	7.2	210 (3.9)	51 (4.0)	0.5
50–59	1416 (26.4)	450 (35.5)	19.8	1519 (28.3)	384 (30.2)	4.3
60–64	1558 (29.0)	441 (34.8)	12.4	1619 (30.2)	394 (31.1)	2.0
≥65	2197 (40.9)	312 (24.6)	35.3	2019 (37.6)	440 (34.7)	6.1
Female, *n* (%)	2731 (50.9)	643 (50.7)	0.4	2740 (51.0)	661 (52.1)	2.1
Region, *n* (%)						
South	2419 (45.1)	680 (53.6)	17.2	2521 (47.0)	627 (49.4)	4.9
Midwest	2078 (38.7)	398 (31.4)	15.4	1993 (37.1)	440 (34.7)	5.0
West	304 (5.7)	65 (5.1)	2.4	297 (5.5)	76 (6.0)	2.0
Northeast	553 (10.3)	123 (9.7)	2.0	544 (10.1)	121 (9.5)	2.0
Unknown	13 (0.2)	2 (0.2)	1.9	12 (0.2)	4 (0.3)	1.9
Year of index date, *n* (%)						

2020		840 (15.7)	88 (6.9)	27.8	748 (13.9)	158 (12.5)	4.3
	Q4	840 (15.7)	88 (6.9)	27.8	748 (13.9)	158 (12.5)	4.3
2021		3609 (67.2)	877 (69.2)	4.1	3618 (67.4)	826 (65.1)	4.8
	Q1	1003 (18.7)	197 (15.5)	8.4	967 (18.0)	213 (16.8)	3.2
	Q2	968 (18.0)	244 (19.2)	3.1	978 (18.2)	216 (17.1)	3.1
	Q3	851 (15.9)	223 (17.6)	4.6	867 (16.1)	205 (16.2)	0.1
	Q4	787 (14.7)	213 (16.8)	5.9	807 (15.0)	192 (15.1)	0.2
2022		918 (17.1)	303 (23.9)	16.9	1001 (18.6)	284 (22.4)	9.3
	Q1	911 (17.0)	293 (23.1)	15.4	988 (18.4)	280 (22.1)	9.2
	Q2	7 (0.1)	10 (0.8)	9.7	13 (0.2)	4 (0.3)	0.7
Insurance plan type[c], *n* (%)							
	PPO	2949 (54.9)	824 (65.0)	20.6	3064 (57.1)	781 (61.6)	9.1
	HMO	2114 (39.4)	348 (27.4)	25.5	1984 (37.0)	415 (32.7)	9.0
	POS	213 (4.0)	68 (5.4)	6.6	225 (4.2)	55 (4.3)	0.6
Indemnity/traditional		15 (0.3)	4 (0.3)	0.7	15 (0.3)	2 (0.2)	1.9
	CDHC	71 (1.3)	23 (1.8)	4.0	74 (1.4)	15 (1.2)	2.0
	Unknown	5 (0.1)	1 (0.1)	0.5	5 (0.1)	1 (0.1)	1.0
Insurance pay type[c], *n* (%)							
	Commercial	3042 (56.7)	979 (77.2)	44.7	3261 (60.8)	823 (64.9)	8.5
	Medicare Advantage	2316 (43.2)	289 (22.8)	44.4	2097 (39.1)	445 (35.1)	8.2
	Medicaid	9 (0.2)	0.0 (0.0)	5.8	9 (0.2)	0.0 (0.0)	5.8

Physician specialty closest to the index date[c], *n* (%)						
Primary care[d]	2479 (46.2)	585 (46.1)	0.1	2491 (46.4)	598 (47.2)	1.5
Respiratory specialist[e]	1329 (24.8)	304 (24.0)	1.8	1311 (24.4)	297 (23.4)	2.3
Allergist	13 (0.2)	4 (0.3)	1.4	14 (0.3)	7 (0.5)	4.2
Pulmonologist	1316 (24.5)	300 (23.7)	2.0	1297 (24.2)	290 (22.9)	3.0
Other	1199 (22.3)	291 (22.9)	1.5	1204 (22.4)	292 (23.1)	1.5
Missing	360 (6.7)	88 (6.9)	0.9	360 (6.7)	80 (6.3)	1.5
Quan-CCI score[f] [1], mean (SD)	2.02 (1.54)	1.95 (1.54)	4.7	2.01 (1.53)	2.03 (1.62)	1.3
Quan-CCI score[f] [1], *n* (%)						
0–2	3644 (67.9)	893 (70.4)	5.5	3666 (68.3)	867 (68.4)	0.1
¾	1298 (24.2)	278 (21.9)	5.4	1279 (23.8)	301 (23.7)	0.2
≥5	425 (7.9)	97 (7.6)	1.0	422 (7.9)	100 (7.9)	0.1
All-cause HRU						
Patients with ≥1 visit during the baseline period excluding the index date[f], n (%)						
Hospitalization	1088 (20.3)	229 (18.1)	5.6	1074 (20.0)	257 (20.3)	0.7
ED visit	2299 (42.8)	511 (40.3)	5.1	2309 (43.0)	527 (41.5)	3.0
OP visit	5352 (99.7)	1263 (99.6)	2.0	5353 (99.7)	1264 (99.7)	1.2
Other visit	2373 (44.2)	466 (36.8)	15.2	2358 (43.9)	451 (35.6)	17.2
Number of HRU events during the baseline period excluding the index date[f], mean (SD)						

Hospitalization	0.28 (0.67)	0.24 (0.62)	5.5	0.27 (0.67)	0.30 (0.76)	3.8
ED visits	0.91 (1.65)	0.88 (1.66)	2.2	0.92 (1.64)	0.95 (1.80)	1.8
OP visits	18.30 (15.93)	18.92 (17.41)	3.7	18.44 (16.73)	19.13 (17.22)	4.1
Other visit	1.43 (4.93)	1.43 (7.85)	0.0	1.40 (4.83)	1.25 (5.96)	2.8
Patients with ≥1 visit on the index date[c], *n* (%)						
Hospitalization	77 (1.4)	8 (0.6)	8.0	72 (1.3)	12 (1.0)	3.3
ED visit	31 (0.6)	3 (0.2)	5.4	33 (0.6)	2 (0.1)	8.2
OP visit	2781 (51.8)	439 (34.6)	35.2	2620 (48.8)	560 (44.2)	9.4
Other visit	75 (1.4)	11 (0.9)	5.0	71 (1.3)	11 (0.9)	4.6
COPD-related HRU[g]						
Patients with ≥1 visit during the baseline period excluding the index date[f], *n* (%)						
Hospitalizations	943 (17.6)	195 (15.4)	5.9	927 (17.3)	224 (17.7)	1.0
ED visit	1380 (25.7)	290 (22.9)	6.6	1367 (25.5)	290 (22.9)	6.0
OP visit	5200 (96.9)	1241 (97.9)	6.2	5206 (97.0)	1241 (97.9)	5.5
Other visit	660 (12.3)	121 (9.5)	8.8	648 (12.1)	116 (9.1)	9.6
Number of HRU events during the baseline period excluding the index date[f], mean (SD)						
Hospitalization	0.23 (0.58)	0.20 (0.53)	5.1	0.22 (0.57)	0.25 (0.65)	4.6
ED visits	0.42 (0.96)	0.39 (0.97)	3.6	0.41 (0.94)	0.40 (1.04)	1.0

OP visits	4.79 (6.50)	5.10 (5.35)	5.3	4.93 (8.31)	5.09 (5.43)	2.3
Other visit	0.22 (1.32)	0.19 (1.48)	1.8	0.21 (1.35)	0.15 (0.97)	5.4
Patients with ≥1 visit on the index date[c], *n* (%)						
Hospitalization	75 (1.4)	8 (0.6)	7.7	70 (1.3)	12 (1.0)	3.0
ED visit	20 (0.4)	1 (0.1)	6.2	21 (0.4)	1 (0.0)	7.6
OP visit	2401 (44.7)	352 (27.8)	35.9	2216 (41.3)	489 (38.5)	5.6
Other visit	50 (0.9)	6 (0.5)	5.5	45 (0.8)	7 (0.5)	4.1
All-cause healthcare costs[f,h], $US 2022, mean (SD)						
Total costs (medical + pharmacy)	22,548.43 (39,019.07)	23,978.48 (42,524.56)	3.5	22,766.76 (39,844.86)	23,409.66 (40,352.83)	1.6
Total medical costs	15,331.11 (34,839.46)	15,888.94 (38,843.20)	1.5	15,600.06 (35,848.93)	15,341.20 (36,517.53)	0.7
IP visit costs	7171.66 (29,243.53)	7001.81 (34,296.23)	0.5	7273.12 (30,255.44)	7054.20 (31,556.00)	0.7
ED visit costs	1332.88 (3881.18)	1504.28 (3977.00)	4.4	1372.52 (4115.43)	1409.77 (3542.81)	1.0
OP visit costs	6826.57 (13,396.55)	7382.85 (14,144.78)	4.0	6954.42 (13,502.74)	6877.24 (12,848.34)	0.6
Other visit costs	541.87 (1930.11)	681.92 (4536.78)	4.0	542.94 (1935.51)	566.95 (3046.05)	0.9
Pharmacy costs	7217.32 (14,939.88)	8089.54 (15,952.39)	5.6	7166.69 (14,894.87)	8068.46 (15,334.26)	6.0
COPD-related healthcare costs[f,g,h], $US 2022, mean (SD)						

Total medical costs	9024.49 (26,734.97)	9097.52 (28,835.95)	0.3	9124.65 (27,468.59)	9000.25 (27,285.87)	0.5
IP visit costs	5756.45 (24,962.51)	5538.91 (27,284.41)	0.8	5779.64 (25,726.00)	5716.88 (25,597.15)	0.2
ED visit costs	819.61 (3126.49)	925.53 (3289.64)	3.3	838.50 (3342.33)	818.69 (2775.29)	0.6
OP visit costs	2448.43 (6375.93)	2633.09 (6979.95)	2.8	2506.51 (6471.19)	2464.68 (6684.30)	0.6
Other visit costs	231.57 (1129.80)	239.59 (984.78)	0.8	228.81 (1139.04)	226.09 (942.16)	0.3

[a]For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the control and the case by the pooled SD of both groups. The pooled SD is the square root of the average of the squared SDs.

[b]For dichotomous variables, the standardized difference was calculated using the following equation where P is the respective proportion of participants in each group: $|(P^{case}-P^{control})| / \sqrt{[(P^{case}(1-Pcase)+P^{control}(1-P^{control}))/2]}$.

[c]Evaluated at the index date (i.e., the date of the first pharmacy claim for single-inhaler FF/UMEC/VI or BUD/GLY/FOR).

[d]Included family medicine practitioner, internal medicine, nurse practitioner, and physician assistant.

[e]Allergist and pulmonologist were not mutually exclusive categories as some patients may have had claims for both specialists on the same day.

[f]Evaluated during the 12-month baseline period, excluding the index date.

[g]COPD-related claims were identified as any claim with a primary or secondary diagnosis of COPD.

[h]Costs were inflated to $US 2022 using the U.S. Medical Care consumer price index from the Bureau of Labor Statistics from the U.S. Department of Labor.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CCI* Charlson comorbidity index, *CDHC* consumer-directed health care, *COPD* chronic obstructive pulmonary disease, *ED* emergency department, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *HMO* health

maintenance organization, *HRU* healthcare resource utilization, *IP* inpatient, *OCS* oral corticosteroid, *OP* outpatient, *POS* point-of-service, *PPO* preferred provider organization, *SCS* systemic corticosteroid, *SD* standard deviation

Table S6 Adherence to FF/UMEC/VI versus BUD/GLY/FOR (weighted analysis)

PDC	FF/UMEC/VI cohort (*n* = 8912)	BUD/GLY/FOR cohort (*n* = 2685)	Percentage point difference between FF/UMEC/VI and BUD/GLY/FOR cohort[a] (95% CI)[b]	Risk ratio[c] (95% CI)[b]	*P* value[b]
Observation period[d], mean (SD)	324.5 (58.3)	320.5 (60.3)			
At 6 months post-index					
PDC, mean (SD)	0.65 (0.31)	0.59 (0.30)	0.07 (0.06, 0.09)	-	<0.001
Patients with PDC ≥0.8, *n* (%)	4064 (45.6)	928 (34.5)	-	1.33 (1.26, 1.42)	<0.001
Patients with PDC ≥0.5, *n* (%)	6398 (71.8)	1725 (64.3)	-	1.15 (1.10, 1.19)	<0.001
At 12 months post-index					
Patients with ≥12 months of follow-up, *n* (%)	5367 (60.2)	1268 (47.2)			
PDC, mean (SD)	0.57 (0.33)	0.50 (0.32)	0.08 (0.05, 0.10)	-	<0.001
Patients with PDC ≥0.8, *n* (%)	1882 (35.1)	314 (24.8)	-	1.43 (1.27, 1.62)	<0.001
Patients with PDC ≥0.5, *n* (%)	2966 (55.3)	582 (45.9)	-	1.22 (1.12, 1.32)	<0.001

[a]Difference in mean PDC was calculated using generalized linear regression models.

[b]CIs and *P* values were generated based on non-parametric bootstrap procedures (B=499).

[c]Risk ratio was calculated using log-binomial regression models.

[d]The observation period spans from the index date until the earliest of 12 months post-index, end of insurance coverage, a diagnosis of asthma, cystic fibrosis, lung cancer, interstitial lung disease, or alpha-1 antitrypsin deficiency, or end of data availability.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CI* confidence interval, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *PDC* proportion of days covered, *SD* standard deviation.

Table S7 Persistence to FF/UMEC/VI versus BUD/GLY/FOR (weighted analysis)

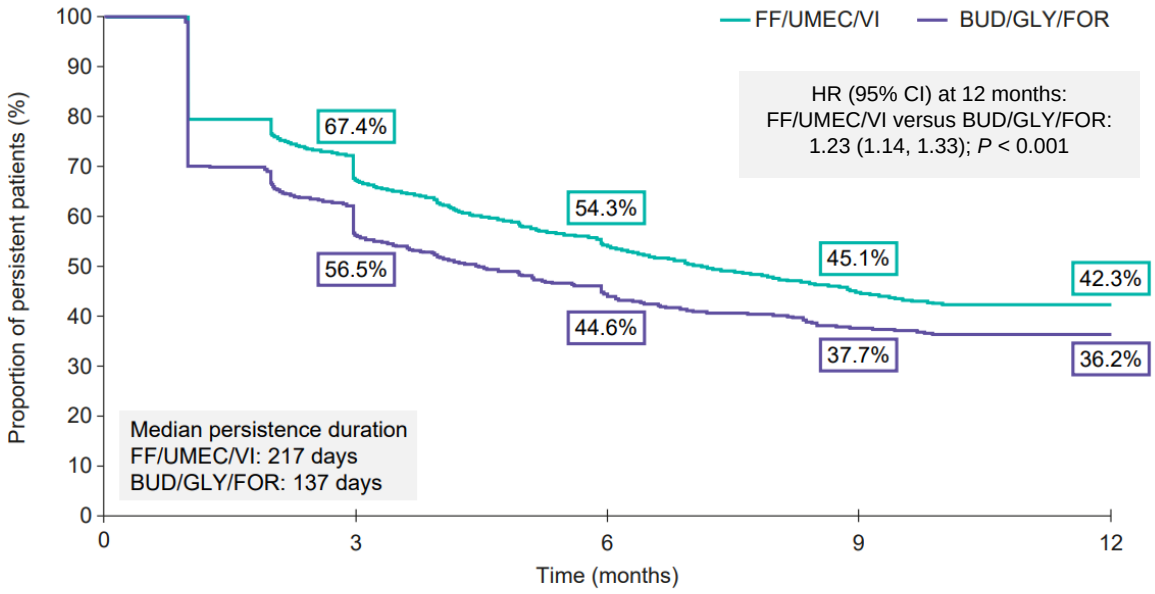
Persistence to triple therapy[a]	Kaplan–Meier estimates		Hazard ratio[b] (95% CI)	*P* value[b]
	FF/UMEC/VI cohort, % (*n* = 8912)	BUD/GLY/FOR cohort, % (*n* = 2685)		
30-day gap				
Time period after the index date				
3 months	56.5	45.8	1.32 (1.24, 1.40)	<0.001
6 months	43.1	32.8	1.30 (1.23, 1.37)	<0.001
9 months	34.8	26.9	1.27 (1.20, 1.33)	<0.001
12 months	31.0	23.6	1.26 (1.20, 1.33)	<0.001
60-day gap				
Time period after the index date				
3 months	66.5	57.9	1.30 (1.22, 1.39)	<0.001
6 months	54.1	45.5	1.27 (1.20, 1.35)	<0.001
9 months	46.3	39.6	1.22 (1.16, 1.29)	<0.001
12 months	43.9	38.2	1.21 (1.14, 1.28)	<0.001
90-day gap				
Time period after the index date				
3 months	70.7	64.8	1.23 (1.14, 1.32)	<0.001
6 months	60.2	54.4	1.20 (1.12, 1.28)	<0.001
9 months	53.7	48.9	1.16 (1.09, 1.24)	<0.001
12 months	53.3	48.6	1.16 (1.09, 1.23)	<0.001

[a]Discontinuation (non-persistence) was identified as a gap of >x days between the end of the days' supply of a dispensing and the following fill or between the end of the days' supply of the last dispensing and the end of follow-up.

[b]Calculated using weighted Cox proportional hazards models.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *SD* standard deviation.

Fig. S1 Kaplan–Meier persistence rates with a 60-day gap[a] – patients with a minimum of 12 months of follow-up (sensitivity analysis)



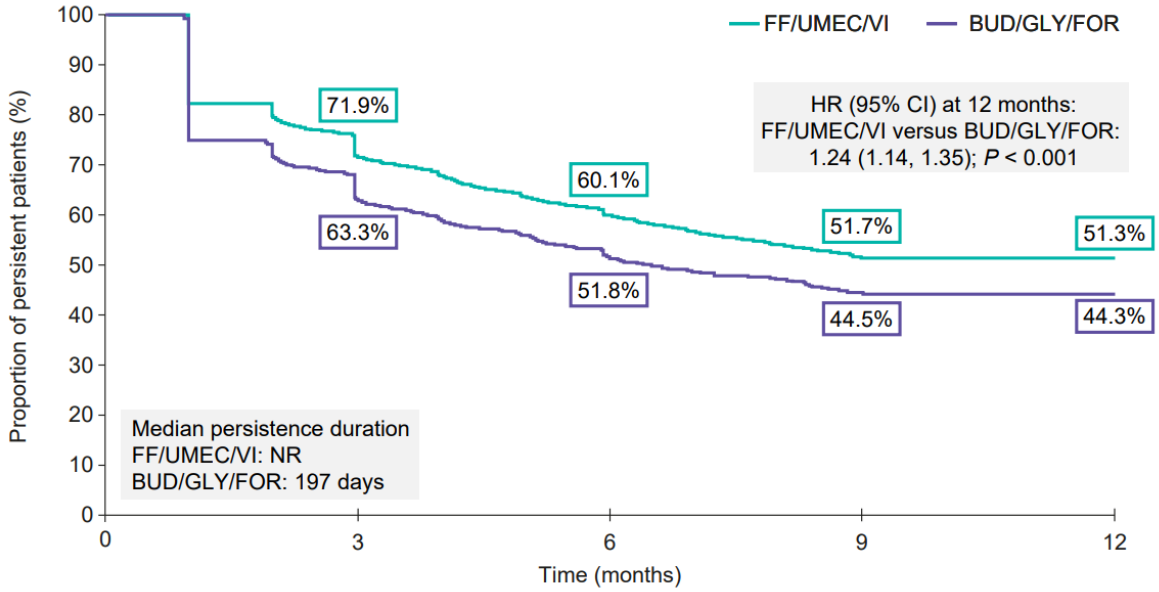
Number of FF/UMEC/VI patients[b]					
At-risk cohort	5367	3619	2914	2422	0
Failed cohort	0	1748	2453	2945	3096
Number of BUD/GLY/FOR patients[b]					
At-risk cohort	1268	716	566	478	0
Failed cohort	0	552	702	790	809

[a]Discontinuation (non-persistence) was identified as a gap of >60 days between the end of the days' supply of a dispensing and the following fill or between the end of the days' supply of the last dispensing and the end of follow-up.

[b]Number of patients still observed at the specific time point.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CI* confidence interval, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *HR* hazard ratio

Fig. S2 Kaplan–Meier persistence rates with a 90-day gap[a] – patients with a minimum of 12 months of follow-up (sensitivity analysis)



Number of FF/UMEC/VI patients[b]					
At-risk cohort	5367	3857	3227	2776	0
Failed cohort	0	1510	2140	2591	2615
Number of BUD/GLY/FOR patients[b]					
At-risk cohort	1268	802	657	565	0
Failed cohort	0	466	611	703	706

[a]Discontinuation (non-persistence) was identified as a gap of >90 days between the end of the days' supply of a dispensing and the following fill or between the end of the days' supply of the last dispensing and the end of follow-up.

[b]Number of patients still observed at the specific time point.

BUD/GLY/FOR budesonide/glycopyrrolate/formoterol fumarate, *CI* confidence interval, *FF/UMEC/VI* fluticasone furoate/umeclidinium/vilanterol, *HR* hazard ratio, *NR* not reached

Reference

1. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–9. doi:10.1097/01.mlr.0000182534.19832.83.