Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD (IMPACT Trial)

DUPLICATE IMPACT

May 14, 2021

NCT02164513

1. RCT Details

This section provides a high-level overview of a **published** RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD (IMPACT Trial)

1.2 Intended aim(s)

To assess the effect of once-daily combination of fluticasone furoate at a dose of 100 ug, umeclidinium at a dose of 62.5ug, and vilanterol at a dose of 25 ug ("triple therapy") versus fluticasone furoate-vilanterol—at doses of 100ug and 25ug, respectively—on the annual rate of moderate or severe COPD exacerbations. (Note: RCT compares additional arm of umeclidinium-vilanterol).

1.3 Primary endpoint for replication

The primary endpoint is the rate of moderate or severe COPD exacerbations defined as an exacerbation leading to treatment with antibiotics or systemic glucocorticoids or one resulting in hospitalization or death.

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

This trial is a superiority trial. Assuming that the annual rate of moderate or severe exacerbation would be 0.80 among patients treated with triple therapy and 0.91 among those treated with fluticasone furoate-vilanterol, it was determined that approximately 4000 patients would be needed in the triple-therapy group and 4000 in the fluticasone furoate-vilanterol group to achieve 90% power to conclude superiority of triple therapy over fluticasone furoate- vilanterol at two sided alpha of 0.01.

1.5 Secondary endpoint for replication (assay sensitivity) and RCT finding

Pneumonia (Hazard ratio, HR=1.02; 95% CI, 0.87-1.19) comparing fluticasone furoate-umeclidinium-vilanterol vs. fluticasone furoate-vilanterol.

1.6 Trial estimate

Rate ratio, RR=0.85 (95% CI, 0.80-0.90) comparing fluticasone furoate-umeclidinium-vilanterol vs. fluticasone furoate-vilanterol during 52 weeks (Lipson et al., 2018).

2. Person responsible for implementation of replication in Aetion

Hemin Lee, MD, MPH, implemented the study design in the Aetion Evidence Platform. She is not responsible for the validity of the design and analytic choices. All implementation steps are recorded, and the implementation history is archived in the platform.

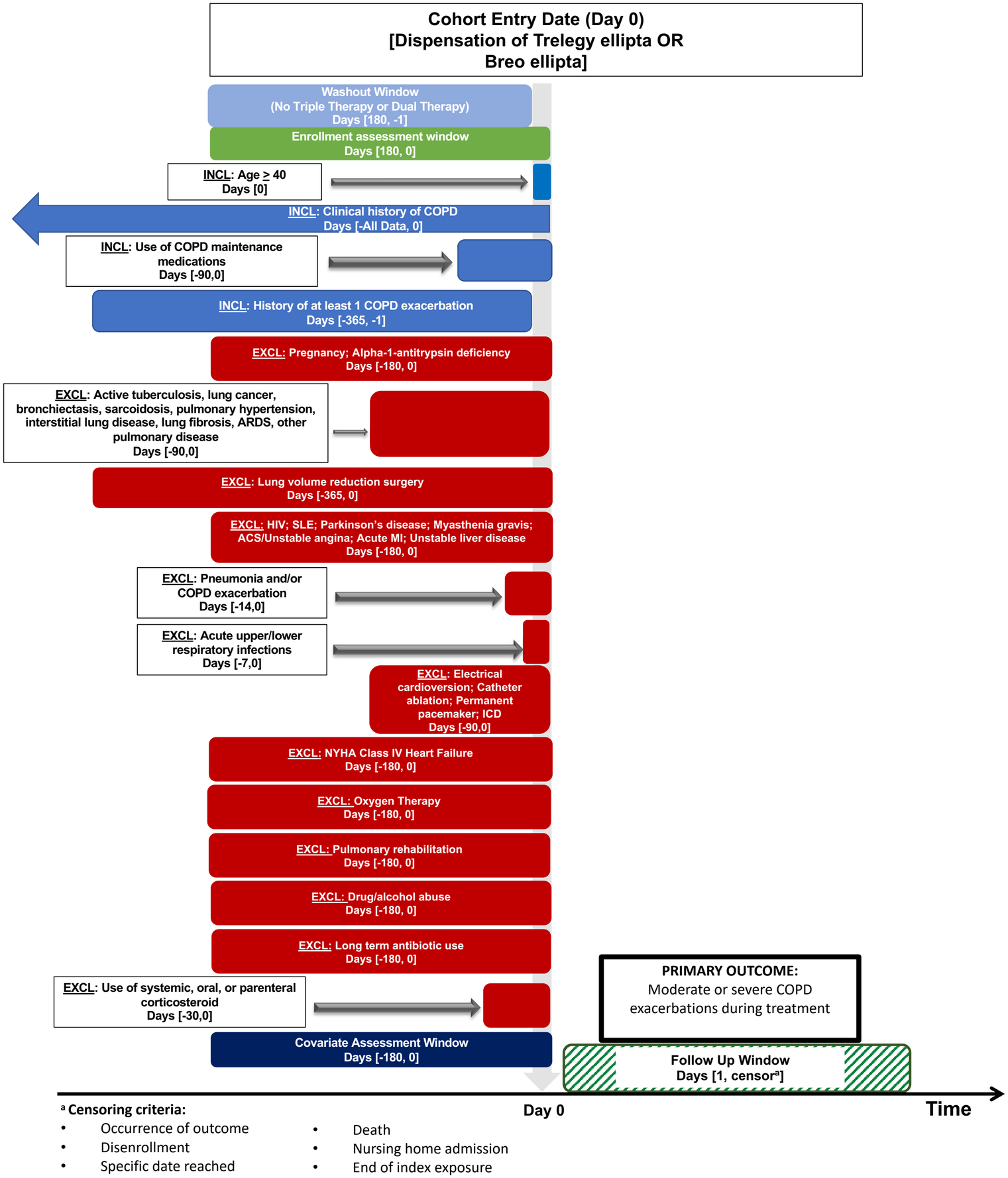
3. Data Source(s)

Optum CDM, IBM® MarketScan®

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Design Diagram – IMPACT TRIAL REPLICATION



[a] **Censoring criteria:**

- Occurrence of outcome
- Disenrollment
- Specific date reached
- Death
- Nursing home admission
- End of index exposure

5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort study design comparing triple therapy to fluticasone furoate-vilanterol users. The patients will be required to have continuous enrollment during a baseline period of 180 days before initiation of triple therapy or fluticasone furoate-vilanterol (index date). We will restrict the analyses to patients with a diagnosis of COPD who have been receiving daily maintenance therapy for at least 3 months prior to index date.

5.2 Important steps for cohort formation

New use of fluticasone furoate-umeclidinium-vilanterol (exposure), and fluticasone furoate-vilanterol (comparator) is defined as no use of either therapy in 180 days prior to index date

5.2.1 Eligible cohort entry dates

Market availability of fluticasone furoate-umeclidinium-vilanterol in the U.S. for management of COPD was approved by FDA on September 18, 2017

- IBM® MarketScan®: September 18, 2017 – December 31, 2018 (end of available data)
- Optum CDM: September 18, 2017 – June 30, 2020 (end of available data)

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

For fluticasone furoate-umeclidinium-vilanterol (triple therapy) vs. fluticasone furoate-vilanterol

FLOWCHART				
	Optum		Marketscan	
Less Excluded Patients	Remaining Patients		Less Excluded Patients	Remaining Patients
All patients		78,202,636		200,203,908

Did not meet cohort entry criteria	-77,961,768	240,868	-200,099,629	104,279
Excluded due to insufficient enrollment	-36,776	204,092	-9,826	94,453
Excluded due to prior use of referent	-91,082	113,010	-57,156	37,297
Excluded due to prior use of exposure	-25,673	87,337	-3,129	34,168
Excluded because patient qualified in >1 exposure category	-10	87,327	-2	34,166
Excluded based on Age : Exclude missing	-1	87,326	0	34,166
Excluded based on Gender: Exclude missing	-3	87,323	0	34,166
Excluded based on INCLUSION: Age >=40	-5,749	81,574	-6,431	27,735
Excluded based on INCLUSION: Established clinical history of COPD	-19,242	62,332	-12,995	14,740
Excluded based on INCLUSION: COPD Maintenance Rx previous 90 days	0	62,332	0	14,740
Excluded based on Exclusion 1 Pregnancy	-12	62,320	-6	14,734
Excluded based on Exclusion 3 - Alpha-1-antitrypsin deficiency	-80	62,240	-35	14,699
Excluded based on Exclusion 4 lung disease including Tb, lung ca, bronchiectasis, sarcoidosis, ILD	-5,546	56,694	-1,166	13,533
Excluded based on Exclusion 5 - Lung volume reduction surgery	0	56,694	0	13,533
Excluded based on Exclusion 6 - HIV/Lupus, Parkinson, MG	-473	56,221	-104	13,429
Excluded based on Exclusion 7 - Pneumonia or COPD exacerbation [-14,0]	-2,191	54,030	-1,321	12,108
Excluded based on Exclusion 8 - Acute upper or lower respiratory infections [-7,0]	-1,335	52,695	-415	11,693
Excluded based on Exclusion 11 - Liver disease	-1,625	51,070	-256	11,437
Excluded based on Excl. 12a - Life threatening cardiac disease	-850	50,220	-97	11,340
Excluded based on Excl 12b Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months	-73	50,147	-37	11,303
Excluded based on Excl. 12c - NYHA Class IV Heart failure	-639	49,508	-148	11,155
Excluded based on Excl. 16 - Oxygen therapy	-1,252	48,256	-47	11,108
Excluded based on Excl. 18 - Pulmonary rehabilitation	-77	48,179	-18	11,090
Excluded based on Excl. 19 - Drug or alcohol abuse	-402	47,777	-103	10,987
Excluded based on Excl. 24a - Use of long term antibiotics >90 days	-280	47,497	-57	10,930
Excluded based on Excl. 24b - Use of corticosteroids [-30,-0]]	-3,211	44,286	-684	10,246
Final cohort		44,286		10,246

6. Variables

6.1 Exposure-related variables:

Study drug:

The study exposure of interest is new initiation of fluticasone furoate-umeclidinium-vilanterol. New initiation will be defined by no use of fluticasone furoate-umeclidinium-vilanterol in the prior 180 days before treatment initiation (washout period).

Comparator agent:

New initiators of fluticasone furoate-vilanterol. New initiation will be defined by no use of fluticasone furoate-vilanterol in the prior 180 days before treatment initiation

6.2 Preliminary Covariates:

- Age
- Gender
- Combined Comorbidity Index (CCI), measured over the baseline covariate assessment period, defined as 180 days prior to and including index date.

Covariates listed above represent only a small subset of covariates that will ultimately be controlled for in the design and analysis. We use the covariates above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (Appendix B).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in Appendix A):

- Primary outcome: Annual rate of moderate or severe COPD exacerbations during treatment
- Control outcome of interest: Pneumonia

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analyses will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real-world databases is expected to be much worse than in the trial, the AT analysis is the primary analysis, as it targets the relative hazard of outcomes on treatment.

The follow-up will start the day after drug initiation (i.e., cohort entry date), as described in the IMPACT, and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest,
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- Nursing home admission
    - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug plus a defined grace period (i.e., 60 days after the end of the last prescription's days' supply in main analyses).

For the intention-to-treat (ITT) analyses, the censoring based on the augmentation/switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7. Initial Feasibility Analysis

Aetion report name:

For fluticasone furoate-umeclidinium-vilanterol vs. fluticasone furoate-vilanterol

Optum CDM -https://bwh-dope.aetion.com/projects/details/1614/results/67127/result/0

IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1615/results/67126/result/0

Date conducted: 03/17/2021

Complete Aetion feasibility analysis using age and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome. No measures of association will be computed nor will incidence rates stratified by treatment group.

8. Initial Power Assessment

Aetion report name:
For fluticasone furoate-umeclidinium-vilanterol vs. fluticasone furoate-vilanterol

Optum CDM - https://bwh-dope.aetion.com/projects/details/1614/results/67129/result/0
IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1615/results/67128/result/0

Date conducted: 03/17/2021

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age , gender, and combined comorbidity index. Power calculations are based on the formulas from Chow et al. (2008).

- Stop analyses until feasibility and power are reviewed by primary investigators and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	3/19/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	
Reasons for stopping analysis (if required):			

9. Balance Assessment

For fluticasone furoate-umeclidinium-vilanterol vs. fluticasone furoate-vilanterol

Optum CDM: https://bwh-dope.aetion.com/projects/details/1614/rwrs/67810

IBM® MarketScan®: https://bwh-dope.aetion.com/projects/details/1615/rwrs/67811

Date conducted: 03/31/2021

10-A. Second Power Assessment

Date conducted: 4/14/2021

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.
    - Pooled

Superiority Analysis	
Number of patients matched	27,512
Reference	13,756
Exposed	13,756
Risk per 1,000 patients	169.90
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	4674.2888
Power	0.999838206

    - Optum CDM

Superiority Analysis	
Number of patients matched	24,142
Reference	12,071
Exposed	12,071
Risk per 1,000 patients	185.24
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	4472.06408
Power	0.999743753

- IBM® MarketScan®

Superiority Analysis	
Number of patients matched	3,370
Reference	1,685
Exposed	1,685
Risk per 1,000 patients	106.86
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	360.1182
Power	0.338233339

- Stop analyses until balance and power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	4/16/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	4/30/2021
Reasons for stopping analysis (if required):			

10-B. Final Power Assessment after Reevaluation of Study Implementation

During a protocol review that occurred after the submission of 2nd feasibility and power analysis, the study team members agree that one inclusion criteria that was marked as "not replicable in claims" could be defined using proxy definitions. A revised cohort was created and with the updated cohort, final feasibility and power analysis was conducted. The study team members confirm that this review was performed prior to the final analysis.

Flowchart of the Revised Study Cohort Assembly

- Revised cohort inclusion highlighted in yellow

	Optum		Marketscan	
Less Excluded Patients	Remaining Patients		Less Excluded Patients	Remaining Patients
All patients		78,779,380		200,203,908
Did not meet cohort entry criteria	-78,538,483	240,897	-200,099,629	104,279
Excluded due to insufficient enrollment	-36,893	204,004	-9,849	94,430
Excluded due to prior use of referent	-102,649	101,355	-60,845	33,585
Excluded due to prior use of exposure	-33,482	67,873	-4,000	29,585
Excluded because patient qualified in >1 exposure category	-10	67,863	-2	29,583
Excluded based on Age : exclude missing	-1	67,862	0	29,583
Excluded based on Gender : exclude missing	-3	67,859	0	29,583
Excluded based on INCLUSION: Age >=40	-5,751	62,108	-6,431	23,152
Excluded based on INCLUSION: Established clinical history of COPD	-19,257	42,851	-12,995	10,157
Excluded based on INCLUSION: COPD Maintenance Rx previous 90 days	0	42,851	0	10,157

Excluded based on Inclusion: COPD exacerbation 1 year prior	-17,279	25,572	-5,381	4,776
Excluded based on Exclusion 1 Pregnancy	-5	25,567	-1	4,775
Excluded based on Exclusion 3 - Alpha-1-antitrypsin deficiency	-39	25,528	-20	4,755
Excluded based on Exclusion 4 lung disease including Tb, lung ca, bronchiectasis, sarcoidosis, ILD	-3,141	22,387	-561	4,194
Excluded based on Exclusion 5 - Lung volume reduction surgery	0	22,387	0	4,194
Excluded based on Exclusion 6 - HIV/Lupus, Parkinson, MG	-250	22,137	-37	4,157
Excluded based on Exclusion 7 - Pneumonia or COPD exacerbation [-14,-0]	-4,339	17,798	-924	3,233
Excluded based on Exclusion 8 - Acute upper or lower respiratory infections [-7,-0]	-233	17,565	-87	3,146
Excluded based on Exclusion 11 - Liver disease	-541	17,024	-72	3,074
Excluded based on Excl. 12a - Life threatening cardiac disease	-311	16,713	-37	3,037
Excluded based on Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months	-19	16,694	-13	3,024
Excluded based on Excl. 12c - NYHA Class IV Heart failure	-216	16,478	-53	2,971
Excluded based on Excl. 16 - Oxygen therapy	-626	15,852	-27	2,944
Excluded based on Excl. 18 - Pulmonary rehabilitation	-36	15,816	-6	2,938
Excluded based on Excl. 19 - Drug or alcohol abuse	-115	15,701	-33	2,905
Excluded based on Excl. 24a - Use of long term antibiotics >90 days	-111	15,590	-21	2,884
Excluded based on Excl. 24b - Use of corticosteroids [-30,0]]	-882	14,708	-271	2,613
Final cohort		14,708		2,613

Balance Assessment of Revised Cohort

After review of previous feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.
  Note- Please refer to **Appendix B**.

- Report covariate balance after matching.
  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	**Referent**	**Exposure**
Dummy outcome	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Start of an additional exposure	220 (2.29%)	186 (1.94%)	34 (0.35%)
End of index exposure	4,220 (44.01%)	2,357 (24.58%)	1,863 (19.43%)
Specified date reached	3,636 (37.92%)	1,525 (15.91%)	2,111 (22.02%)
End of patient data	0 (0.0%)	0 (0.0%)	0 (0.0%)
End of patient enrollment	828 (8.64%)	409 (4.27%)	419 (4.37%)
Nursing home admission, pharmacy disenrollment	684 (7.13%)	317 (3.31%)	367 (3.83%)

- Report follow-up time by treatment group.

Median Follow-Up Time (Days) [IQR]		
Patient Group	**Optum**	**Marketscan**
Overall Patient Population	131 [88, 240]	107.5 [72.5, 177]
Referent	119 [88, 211.5]	108 [86, 170]
Exposure	146 [88,271]	107 [61, 188]

- Report overall risk of the primary outcome.

	Optum CDM	**IBM® MarketScan®**	**Pooled**
Risk per 1,000 patients	292.82	202.84	278.6

Final Power Assessment
Optum: https://bwh-dope.aetion.com/projects/details/1614/rwrs/69652
Marketscan: https://bwh-dope.aetion.com/projects/details/1615/rwrs/69653
Date conducted: 5/6/2021

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in above section. All other parameters in the table should be the same as in Section 8.
    - Pooled

Superiority Analysis	
Number of patients matched	9,588
Reference	4,794
Exposed	4,794
Risk per 1,000 patients	278.60
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	2671.2168
Power	0.987449189

- Optum CDM

Superiority Analysis	
Number of patients matched	8,496
Reference	4,248
Exposed	4,248
Risk per 1,000 patients	292.82
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	2487.79872
Power	0.981829103

- IBM® MarketScan®

Superiority Analysis	
Number of patients matched	1,092
Reference	546
Exposed	546
Risk per 1,000 patients	202.84
Desired HR from RCT	0.85
Alpha (2-sided)	0.05
Number of events expected	221.50128
Power	0.227214863

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	5/12/2021
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:
Date votes and concerns are summarized:

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.
- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the success of the RWD study in the Google Form. This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.
- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

12. Register study protocol on clinicalTrials.gov

Date conducted:

- Register the study on clinicalTrials.gov and upload this document.

13. Comparative Analyses

Aetion report name:
Date conducted:

a. For primary analysis:

b. For sensitivity analyses:

14. Requested Results

a. Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	**Exposure**	**Std. diff.**	**Referent**	**Exposure**	**Std. diff.**
Number of patients			-			-
Age categories						
…						

b. Table 2: Follow-up time

Patient Group	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	
Referent	
Exposure	

c. Table 3: Censoring events

	Overall	**Referent**	**Exposure**
Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
…			

d. Table 4: Results from primary analyses;

Analysis	**No. exposed events**	**No. referent events**	**Exposed rate**	**Referent rate**	**HR (95% CI)**
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

e. Table 5: Results from secondary analyses.

15. References

Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med. 2018 May 3;378(18):1671-1680. doi: 10.1056/NEJMoa1713901. Epub 2018 Apr 18. PMID: 29668352.

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 177.

Appendix A

#	IMPACT trial definitions	Implementation in routine care	References	Color Coding
	Trial details- clinicaltrials.gov NCT02164513		**Please see the following Google Drive for further details or any missing information:** https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV?usp=sharing	Criteria
	EXPOSURE vs. COMPARISON		**ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/ backward mapping based on the CMS ICD-9 to ICD-10 mapping:** https://www.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html	Adequate mapping in claims
	Triple Therapy (100 µg fluticasone furoate, 62.5 µg umeclidinium [LAMA], 25 µg vilanterol [LABA]) vs. Dual Therapy (100 µg fluticasone furoate, 25 µg vilanterol [LABA] OR 62.5 µg umeclidinium [LAMA], 25 µg vilanterol [LABA])	**Exposure** 100 µg fluticasone furoate, 62.5 µg umeclidinium, 25 µg vilanterol (Trelegy ellipta) **Referent** 100 µg fluticasone furoate, 25 µg vilanterol 6 (Breo ellipta)		Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or can't be measured in claims
	Annual rate of moderate or severe COPD exacerbations during treatment	**Measured 1 day after drug initiation in primary diagnosis position and inpatient care setting:** Moderate exacerbation COPD diagnosis code occuring in inpatient any position or outpatient setting accompanied by a prescription claim for systemic steroid occuring 14 days before or after the COPD diagnosis code. Severe exacerbation COPD diagnosis code occuring in inpatient primary position COPD ICD-9: 491.*, 492.*, 496.0 ICD-10: J41.*, J42. * J43.*, J44.*	Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data. Int J Chron Obstruct Pulmon Dis. 2018;13:2121-2130. Published 2018 Jul 11. doi:10.2147/COPD.S155773 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6805625/	Can't be measured in claims but not important for the analysis
	INCLUSION CRITERIA			
1	Informed Consent: A signed and dated written informed consent prior to study participation	N/A		
2	Age ≥ 40	**Measured on the day of drug initiation:** Age >=40		
3	An established clinical history of COPD in accordance with the definition by the ATS/ERS	**Measure any time prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** COPD ICD-9: 491.*, 492.*, 496.0 ICD-10: J41.*, J42. * J43.*, J44.*	Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data. Int J Chron Obstruct Pulmon Dis. 2018;13:2121-2130. Published 2018 Jul 11. doi:10.2147/COPD.S155773 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6805625/	
4	Current or former cigarette smokers with a history of cigarette smoking of 10 pack-years at screening (visit 1) [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1	N/A		
5	A score of ≥10 on the COPD Assessment Test (CAT) at screening.	N/A		
6	A post-albuterol/salbutamol FEV1/FVC ratio of <0.70 at screening.	N/A		

Appendix A

7	Receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening.	**Measured 90 days prior to and including day of drug initiation with at least 1 dispensing of following COPD maintenance medications:** LABA indacaterol maleate, olodaterol hcl, salmeterol xinafoate, arformoterol tartrate, formoterol fumarate, terbutaline sulfate LAMA aclidinium bromide, umeclidinium bromide, tiotropium bromide, glycopyrrolate LABA/LAMA tiotropium bromide/olodaterol hcl, indacaterol maleate/glycopyrrolate, glycopyrrolate/formoterol fumarate, umeclidinium bromide/vilanterol trifenatate LABA/ICS mometasone furoate/formoterol fumarate, budesonide/formoterol fumarate, fluticasone furoate/vilanterol trifenatate, fluticasone propionate/salmeterol xinafoat LAMA/LABA/ICS fluticasone furoate/umeclidinium bromide/vilanterol trifenat	
8	A post-bronchodilator FEV1 < 50% predicted normal and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months OR a post-bronchodilator 50% ≤FEV1 < 80% predicted normal and a documented history of ≥ 2 moderate exacerbations or a documented history of ≥1 severe COPD exacerbation (hospitalized) in the previous 12 months.	**Measured 365 days prior to drug initiation (excluding cohort entry date) , occurring at least once:** Moderate exacerbation COPD diagnosis code occuring in inpatient any position or outpatient setting accompanied by a prescription claim for systemic steroid occuring 14 days before or after the COPD diagnosis code. Severe exacerbation COPD diagnosis code occuring in inpatient primary position COPD ICD-9: 491.*, 492.*, 496.0 ICD-10: J41.*, J42. * J43.*, J44.*	Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data. Int J Chron Obstruct Pulmon Dis. 2018;13:2121-2130. Published 2018 Jul 11. doi:10.2147/COPD.S155773 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6805625/
	alanine aminotransferase (ALT) <2x upper limit of normal (ULN); alkaline phosphatase ≤1.5xULN; bilirubin ≤1.5xULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)	**Applied in exclusion criteria (see severe liver disease)**	
	EXCLUSION CRITERIA		
1	Pregnacy or child bearing potential without acceptable contraceptive method	**Measured 180 days prior to and including day of drug initiation in any position or any care setting:** See codes in 'Pregnancy' tab	
2	Asthma - subjects with prior history of asthma are eligible if they have a current diagnosis of COPD	N/A	
3	Subjects with α1-antitrypsin deficiency as the underlying cause of COPD	**Measured 180 days prior to and including day of drug initiation in any position or any care setting:** Alpha-1-antitrypsin deficiency ICD-9: 273.4 ICD-10: E88.01	

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4	Subjects with active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases	**Measured 90 days prior to and including day of drug initiation in any position or any care setting:** Tuberculosis ICD-9: 010.x - 018.x ICD-10: A15.x - A19.x Lung cancer ICD-9: 162.2x, 162.3x, 162.4x, 162.5x, 162.8x, 162.9x ICD-10: C34.0x, C34.1x, C34.2x, C34.3x, C34.8x, C34.9x Bronchiectasis ICD-9: 494.x ICD-10: J47.x Sarcoidosis ICD-9 135.x ICD-10: D86.x ICD-9: 515.x, 516.3, 516.8, 516.9, 517.1, 517.8, 518.89 Pulmonary hypertension ICD-10: I27.0, I27.20 ICD-9: 416.0 Interstitial lung disease, lung fibrosis, ARDS ICD-9: 515.x 516.x, 517.x, 518.8x ICD-10: J84.x, J80.x Other pulmonary disease ICD-9: 416.x ICD-10: I27.x	
5	Subjects with lung volume reduction surgery within the 12 months prior to screening	**Measured 365 days prior to and including day of drug initiation in any position or any care setting:** CPT code: 32491 32672 HCPCS code: G0305	Decker MR, Leverson GE, Jaoude WA, Maloney JD. Lung volume reduction surgery since the National Emphysema Treatment Trial: study of Society of Thoracic Surgeons Database. J Thorac Cardiovasc Surg. 2014;148(6):2651-8.e1. doi:10.1016/j.jtcvs.2014.02.005
6	Immune suppression (e.g. HIV, Lupus) or other risk factors for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis)	**Measured 180 days prior to and including ay of drug initiation in any position or any care setting:** HIV ICD-9: 042.x Human immunodeficiency virus [HIV] disease 079.53 Human immunodeficiency virus, type 2 [HIV-2] V08 Asymptomatic human immunodeficiency virus [HIV] infection status ICD-10: B20.x Human immunodeficiency virus [HIV] disease B97.35 Human immunodeficiency virus, type 2 [HIV-2] Z21.x Asymptomatic human immunodeficiency virus [HIV] infection status SLE ICD-9: 710.0 ICD-10: M32.x Parkinson's disease ICD-9-CM: 332.x ICD-10-CM: G20, G21.xx Myasthenia gravis ICD-9: 358.0x ICD-10: G70.0x	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119

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7	Pneumonia and/or moderate or severe COPD exacerbation that has not resolved at least 14 days prior to Screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable). In addition, any subject that experiences pneumonia and/or moderate or severe COPD exacerbation during the run-in period will be excluded	**Measured 14 days prior to and inlcuding day of drug initiation in any position or any care setting:** Pneumonia and or COPD exacerbation <u>Pnuemonia</u> ICD9: 480.x, 481.x, 482.x, 483.x, 484.x, 485.x, 486.x ICD-10: J12.x, J13.x, J14.x, J15.x, J16.x, J17.x, J18.x <u>COPD exacerbation</u> Moderate exacerbation COPD diagnosis code occuring in inpatient or outpatient setting, any position. For outpatient COPD diagnosis, it is accompanied by a prescription claim for systemic steroid occuring 14 days before or after the COPD diagnosis code. <u>Severe exacerbation</u> COPD diagnosis code occuring in inpatient primary position <u>COPD</u> "491.0", "491.1", "491.2", "491.21", "491.22", "491.8", "491.9", "492.0", "J41.8", "J43.1", "J43.8", "J47.0", "491.20", "492.8", "494.0", "494.1", "506.4", "J41.0", "J41.1", "J43.0", "J43.2", "J43.9", "J44.0", "J44.1", "J47.1", "J47.9"	
8	Other Respiratory tract infections that have not resolved at least 7 days prior to screening	**Measured 7 days prior to and including day of drug initiation in any position or any care setting:** <u>Acute upper /lower respiratory infections</u> ICD-9: 460.x, 461.x, 462.x, 463.x, 464.x, 461 ICD-10: J00.x, J01.x, J02.x, J03.x, J04.x, J05.x, J06.x, J20.x, J21.x, J22.x	Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177
9	Chest x-ray (posteroanterior and lateral) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on CXR (e.g. significant cardiomegaly, pleural effusion or scarring). All subjects will have a chest x-ray at Screening Visit 1 (or historical radiograph or CT scan obtained within 3 months prior to screening) that will be over-read by a central vendor.	N/A	
10	Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled	N/A	
11	Unstable liver disease as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Note: Chronic stable hepatitis B and C are acceptable if the subject otherwise meets entry criteria	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** See codes in 'Liver disease' tab	
12a	Unstable or life threatening cardiac disease: subjects with any of the following at Screening (Visit 1) would be excluded: Myocardial infarction or unstable angina in the last 6 months	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** <u>ACS/unstable angina</u> ICD-9: 411.xx <u>Acute MI</u> ICD-9: 410.X (acute myocardial infarction) excluding 410.x2 (subsequent episode of care)	
12b	Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months	**Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** <u>Electrical cardioversion</u> CPT: 92960, 92961 <u>Catheter ablation</u> CPT: 93650, 93653, 93654 93655,, 93656, 93657, 93462 <u>Permanent pacemaker</u> CPT: 33202-33249 <u>Implantable cardioverter-defibrillator (ICD)</u> ICD-9: 00.51, 00.54, 37.94 - 37.98 ICD-10: 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ, 0JH609Z, 0JH639Z, 0JH809Z, 0JH839Z CPT-4: 33220, 33223, 33230, 33231, 33240 - 33249, 33270, 93640 - 93642,	American Medical Association, Current Procedural Terminology (CPT). Professional Edition. Chicago, IL. https://www.amaassn.org/practice-management/cpt-current-procedural-terminology * https://www.cms.gov/Outreach-and-Education/MedicareLearning-Network-MLN/MLNProducts/AMA-Disclaimer.html

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12c	NYHA Class IV Heart failure	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Systolic HF ICD-9: 428.2x ICD-10: I50.2x Combined Systolic/Diastolic HF ICD-9: 428.4x ICD-10: I50.4x	
13	Abnormal and clinically significant 12-Lead ECG finding: - AF with rapid ventricular rate >120 BPM - sustained or nonsustained VT - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted) - QTcF ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥ 120 msec	N/A	
14	**Contraindications:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction	N/A	
15	**Cancer:** Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma in situ of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment	N/A	
16	**Oxygen therapy:** Use of long-term oxygen therapy (LTOT) described as resting oxygen therapy >3L/min (Oxygen use less than or equal to 3L/min flow is not exclusionary.)	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Home oxygen use HCPCS: E0424, E0441, E0443, ICD-10: Z99.81 ICD-9: V46. 2	
17	**Medication prior to spirometry:** Subjects who are medically unable to withhold their albuterol/salbutamol for the 4-hour period required prior to spirometry testing at each study visit	N/A	
18	**Pulmonary rehabilitation:** Subjects who have participated in the acute phase of a Pulmonary Rehabilitation Program within 4 weeks prior to Screening or subjects who plan to enter the acute phase of a Pulmonary Rehabilitation Program during the study. Subjects who are in the maintenance phase of a Pulmonary Rehabilitation Program are not excluded	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Pulmonary rehabilitation CPT/HCPCS: G0237, G0238, G0239, G0424,S9473, 94669	https://www.modahealth.com/pdfs/med_criteria/PulmonaryRehab.pdf
19	**Drug/alcohol abuse:** Subjects with a known or suspected history of alcohol or drug abuse	**Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting:** Alcohol abuse or dependence 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x, V11.3x Drug abuse or dependence 292.xx, 304.xx, 305.2x-305.9x, 648.3x	Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119
20	**Non-compliance:** Subjects at risk of non-compliance, or unable to comply with the study procedures - any infirmity, disability, or geographic location that would limit compliance for scheduled visit.	N/A	
21	**Questionable validity of consent**: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study	N/A	
22	**Affiliation with investigator site**: Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned that is involved with this study	N/A	
23	**Inability to read:** Any subject who is unable to read and/or would not be able to complete study related materials	N/A	
24a	**The use of any of the following medications under the given conditions:** - Long term antibiotic use (short term antibiotics are allowed if treating short-term acute infection or short-term exacerbation	**Measured 180 days prior to and including day of drug initiation, with days supply exceeding >90 days:** See codes in 'Antibiotics' tab	
24b	Use of a systemic, oral, or parenteral corticosteroid in the last 30 days (except unless treating COPD exacerbations/pneumonia)	**Measured 30 days prior to and including day of drug initiation:** Cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone	
24c	Use of any other investigational drug within the last 30 days or 5 half-lives (whichever is longer)	N/A	

Appendix A

Pregnancy
Diagnosis codes
650 NORMAL DELIVERY
660 OBSTRUCTED LABOR
661 ABNORMALITY OF FORCES OF LABOR
662 LONG LABOR
663 UMBILICAL CORD COMPLICATIONS DURING LABOR AND DELIVERY
664 TRAUMA TO PERINEUM AND VULVA DURING DELIVERY
665 OTHER OBSTETRICAL TRAUMA
667 RETAINED PLACENTA OR MEMBRANES WITHOUT HEMORRHAGE
668 COMPLICATIONS OF THE ADMINISTRATION OF ANESTHETIC OR OTHER SEDATION IN LABOR AND DELIVERY
669.94 UNSPECIFIED COMPLICATION OF LABOR AND DELIVERY POSTPARTUM CONDITION OR COMPLICATION
V24 POSTPARTUM CARE AND EXAMINATION
V24.0 POSTPARTUM CARE AND EXAMINATION IMMEDIATELY AFTER DELIVERY
V24.1 POSTPARTUM CARE AND EXAMINATION OF LACTATING MOTHER
V24.2 ROUTINE POSTPARTUM FOLLOW
V27 OUTCOME OF DELIVERY
V27.0 MOTHER WITH SINGLE LIVEBORN
V27.1 MOTHER WITH SINGLE STILLBORN+A2:J81
V27.2 MOTHER WITH TWINS BOTH LIVEBORN
V27.3 MOTHER WITH TWINS ONE LIVEBORN AND ONE STILLBORN
V27.4 MOTHER WITH TWINS BOTH STILLBORN
V27.5 MOTHER WITH OTHER MULTIPLE BIRTH ALL LIVEBORN
V27.6 MOTHER WITH OTHER MULTIPLE BIRTH SOME LIVEBORN
V27.7 MOTHER WITH OTHER MULTIPLE BIRTH ALL STILLBORN
V27.9 MOTHER WITH UNSPECIFIED OUTCOME OF DELIVERY

Appendix A

Procedure codes

72.0 LOW FORCEPS OPERATION
72.1 LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2 MID FORCEPS OPERATION
72.21 MID FORCEPS OPERATION WITH EPISIOTOMY
72.29 OTHER MID FORCEPS OPERATION
72.3 HIGH FORCEPS OPERATION
72.31 HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39 OTHER HIGH FORCEPS OPERATION
72.4 FORCEPS ROTATION OF FETAL HEAD
72.5 BREECH EXTRACTION
72.51 PARTIAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.52 OTHER PARTIAL BREECH EXTRACTION
72.53 TOTAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.54 OTHER TOTAL BREECH EXTRACTION
72.6 FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7 VACUUM EXTRACTION
72.71 VACUUM EXTRACTION WITH EPISIOTOMY
72.79 OTHER VACUUM EXTRACTION
72.8 OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9 UNSPECIFIED INSTRUMENTAL DELIVERY
73.0 ARTIFICIAL RUPTURE OF MEMBRANES
73.01 INDUCTION OF LABOR BY ARTIFICIAL RUPTURE OF MEMBRANES
73.09 OTHER ARTIFICIAL RUPTURE OF MEMBRANES
73.1 OTHER SURGICAL INDUCTION OF LABOR
73.2 INTERNAL AND COMBINED VERSION AND EXTRACTION
73.21 INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
73.22 INTERNAL AND COMBINED VERSION WITH EXTRACTION
73.3 FAILED FORCEPS
73.4 MEDICAL INDUCTION OF LABOR

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73.5 MANUALLY ASSISTED DELIVERY
73.51 MANUAL ROTATION OF FETAL HEAD
73.59 OTHER MANUALLY ASSISTED DELIVERY
73.6 EPISIOTOMY
73.8 OPERATIONS ON FETUS TO FACILITATE DELIVERY
73.9 OTHER OPERATIONS ASSISTING DELIVERY
73.91 EXTERNAL VERSION ASSISTING DELIVERY
73.92 REPLACEMENT OF PROLAPSED UMBILICAL CORD
73.93 INCISION OF CERVIX TO ASSIST DELIVERY
73.94 PUBIOTOMY TO ASSIST DELIVERY
73.99 OTHER OPERATIONS ASSISTING DELIVERY
74.0 CLASSICAL CESAREAN SECTION
74.1 LOW CERVICAL CESAREAN SECTION

Appendix A

Liver Disease
070.0 - VIRAL HEPATITIS A WITH HEPATIC COMA
070.2 - VIRAL HEPATITIS B WITH HEPATIC COMA
070.22 - CHRONIC VIRAL HEPATITIS B WITH HEPATIC COMA WITHOUT HEPATITIS DELTA
070.23 - CHRONIC VIRAL HEPATITIS B WITH HEPATIC COMA WITH HEPATITIS DELTA
070.3 - VIRAL HEPATITIS B WITHOUT MENTION OF HEPATIC COMA
070.30 - VIRAL HEPATITIS B WITHOUT HEPATIC COMA ACUTE OR UNSPECIFIED WITHOUT HEPATITIS DELTA
070.31 - VIRAL HEPATITIS B WITHOUT HEPATIC COMA ACUTE OR UNSPECIFIED WITH HEPATITIS DELTA
070.32 - CHRONIC VIRAL HEPATITIS B WITHOUT HEPATIC COMA WITHOUT HEPATITIS DELTA
070.41 - ACUTE HEPATITIS C WITH HEPATIC COMA
070.43 - HEPATITIS E WITH HEPATIC COMA
070.44 - CHRONIC HEPATITIS C WITH HEPATIC COMA
070.49 - OTHER SPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA
070.51 - ACUTE HEPATITIS C WITHOUT MENTION OF HEPATIC COMA
070.54 - CHRONIC HEPATITIS C WITHOUT HEPATIC COMA
070.6 - UNSPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA
070.7 - UNSPECIFIED VIRAL HEPATITIS C
070.70 - UNSPECIFIED VIRAL HEPATITIS C WITHOUT HEPATIC COMA
070.71 - UNSPECIFIED VIRAL HEPATITIS C WITH HEPATIC COMA
456.1 - ESOPHAGEAL VARICES WITHOUT BLEEDING
456.2 - ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE
570 - ACUTE AND SUBACUTE NECROSIS OF LIVER
571.0 - ALCOHOLIC FATTY LIVER
571.1 - ACUTE ALCOHOLIC HEPATITIS
571.3 - ALCOHOLIC LIVER DAMAGE UNSPECIFIED
571.40 - CHRONIC HEPATITIS UNSPECIFIED
571.41 - CHRONIC PERSISTENT HEPATITIS
571.49 - OTHER CHRONIC HEPATITIS
571.5 - CIRRHOSIS OF LIVER WITHOUT ALCOHOL
571.6 - BILIARY CIRRHOSIS
571.9 - UNSPECIFIED CHRONIC LIVER DISEASE WITHOUT ALCOHOL
572.0 - ABSCESS OF LIVER

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572.2 - HEPATIC ENCEPHALOPATHY
572.3 - PORTAL HYPERTENSION
572.8 - OTHER SEQUELAE OF CHRONIC LIVER DISEASE
573.1 - HEPATITIS IN VIRAL DISEASES CLASSIFIED ELSEWHERE
573.8 - OTHER SPECIFIED DISORDERS OF LIVER
573.9 - UNSPECIFIED DISORDER OF LIVER
789.51 - MALIGNANT ASCITES
B15.0
B16.0
B17.10
B17.11
B17.9
B18.2
B18.9
B19.11
B19.20
B25.1
I85.00
I85.10
K70.11
K70.2
K70.30
K70.31
K70.40
K70.9
K71.0
K71.10
K71.11
K71.3
K71.50
K71.8
K71.9

Appendix A

K72.01
K72.11
K73.1
K73.9
K74.3
K74.4
K74.5
K74.60
K74.69
K75.0
K75.89
K76.2
K76.4
K76.81
K76.89
K76.9
K77
K83.5
R17
R18.8
070.1 - VIRAL HEPATITIS A WITHOUT HEPATIC COMA
070.20 - VIRAL HEPATITIS B WITH HEPATIC COMA ACUTE OR UNSPECIFIED WITHOUT HEPATITIS DELTA
070.21 - VIRAL HEPATITIS B WITH HEPATIC COMA ACUTE OR UNSPECIFIED WITH HEPATITIS DELTA
070.33 - CHRONIC VIRAL HEPATITIS B WITHOUT HEPATIC COMA WITH HEPATITIS DELTA
070.4 - OTHER SPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA
070.42 - HEPATITIS DELTA WITHOUT ACTIVE HEPATITIS B DISEASE WITH HEPATIC COMA HEPATITIS DELTA WITH HEPATITIS B CARRIER STATE
070.5 - OTHER SPECIFIED VIRAL HEPATITIS WITHOUT MENTION OF HEPATIC COMA
070.52 - HEPATITIS DELTA WITHOUT ACTIVE HEPATITIS B DISEASE OR HEPATIC COMA
070.53 - HEPATITIS E WITHOUT HEPATIC COMA
070.59 - OTHER SPECIFIED VIRAL HEPATITIS WITHOUT HEPATIC COMA
070.9 - UNSPECIFIED VIRAL HEPATITIS WITHOUT HEPATIC COMA
456.0 - ESOPHAGEAL VARICES WITH BLEEDING

Appendix A

456.20 - ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE WITH BLEEDING
456.21 - ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE WITHOUT BLEEDING
571.2 - ALCOHOLIC CIRRHOSIS OF LIVER
571.4 - CHRONIC HEPATITIS
571.42 - AUTOIMMUNE HEPATITIS
571.8 - OTHER CHRONIC NONALCOHOLIC LIVER DISEASE
572.1 - PORTAL PYEMIA
572.4 - HEPATORENAL SYNDROME
573.0 - CHRONIC PASSIVE CONGESTION OF LIVER
573.2 - HEPATITIS IN OTHER INFECTIOUS DISEASES CLASSIFIED ELSEWHERE
573.3 - HEPATITIS UNSPECIFIED
573.4 - HEPATIC INFARCTION
573.5 - HEPATOPULMONARY SYNDROME
576.8 - OTHER SPECIFIED DISORDERS OF BILIARY TRACT
782.4 - JAUNDICE UNSPECIFIED NOT OF NEWBORN
789.5 - ASCITES
789.59 - OTHER ASCITES
B15.9
B16.1
B16.2
B16.9
B17.0
B17.2
B17.8
B18.0
B18.1
B18.8
B19.0
B19.10
B19.21
B19.9
I85.01

Appendix A

I85.11
K70.0
K70.10
K70.41
K71.2
K71.4
K71.51
K71.6
K71.7
K72.00
K72.10
K72.90
K72.91
K73.0
K73.2
K73.8
K74.0
K74.1
K74.2
K75.1
K75.2
K75.3
K75.4
K75.81
K75.9
K76.0
K76.1
K76.3
K76.5
K76.6
K76.7
K83.8

K87 R18.0

Appendix A

Antibiotics
ALATROFLOXACIN MESYLATE
AMIKACIN
AMIKACIN SULFATE
AMIKACIN SULFATE IN 0.9 % SODIUM CHLORIDE
AMIKACIN SULFATE/PF
AMOXICILLIN
AMOXICILLIN/POTASSIUM CLAVULANATE
AMPICILLIN ANHYDROUS
AMPICILLIN SODIUM
AMPICILLIN SODIUM/SULBACTAM SODIUM
AMPICILLIN TRIHYDRATE
AZITHROMYCIN
AZITHROMYCIN HYDROGEN CITRATE
AZTREONAM
AZTREONAM LYSINE
AZTREONAM/DEXTROSE-WATER
BACAMPICILLIN HCL
BACITRACIN
BACITRACIN ZINC
BACITRACIN ZINC MICRONIZED
BACITRACIN ZINC/POLYMYXIN B SULFATE
BACITRACIN ZINC/POLYMYXIN B SULFATE/PRAMOXINE
BACITRACIN, MICRONIZED
BACITRACIN/DIMETHICONE/ZINC OXIDE
BACITRACIN/LIDOCAINE
BACITRACIN/POLYMYXIN B SULFATE
BACITRACIN/POLYMYXIN B SULFATE/LIDOCAINE
BACITRACIN/PRAMOXINE HCL/ALOE VERA
BISMUTH SUBSALICYLATE/METRONIDAZOLE/TETRACYCLINE HCL
CARBENICILLIN INDANYL SODIUM
CEFACLOR

Appendix A

CEFADROXIL
CEFAMANDOLE NAFATE
CEFAMANDOLE NAFATE/DEXTROSE 5 % IN WATER
CEFAZOLIN SODIUM
CEFAZOLIN SODIUM IN 0.9 % SODIUM CHLORIDE
CEFAZOLIN SODIUM/DEXTROSE 5 % IN WATER
CEFAZOLIN SODIUM/DEXTROSE, ISO-OSMOTIC
CEFAZOLIN SODIUM/WATER FOR INJECTION,STERILE
CEFDINIR
CEFDITOREN PIVOXIL
CEFEPIME HCL
CEFEPIME HCL IN DEXTROSE 5 % IN WATER
CEFEPIME HCL IN ISO-OSMOTIC DEXTROSE
CEFIXIME
CEFONICID SODIUM
CEFOPERAZONE SODIUM
CEFOPERAZONE SODIUM/DEXTROSE 2.4 %-WATER
CEFOTAXIME SODIUM
CEFOTAXIME SODIUM/DEXTROSE 5 % IN WATER
CEFOTAXIME SODIUM/DEXTROSE, ISO-OSMOTIC
CEFOTETAN DISODIUM
CEFOTETAN DISODIUM IN ISO-OSMOTIC DEXTROSE
CEFOTETAN IN DEXTROSE
CEFOXITIN SODIUM
CEFOXITIN SODIUM/DEXTROSE 5 % IN WATER
CEFOXITIN SODIUM/DEXTROSE, ISO-OSMOTIC
CEFPODOXIME PROXETIL
CEFPROZIL
CEFTAROLINE FOSAMIL ACETATE
CEFTAZIDIME
CEFTAZIDIME IN DEXTROSE 5% AND WATER
CEFTAZIDIME IN DEXTROSE, ISO-OSMOTIC

Appendix A

CEFTAZIDIME SODIUM
CEFTAZIDIME SODIUM IN 0.9 % SODIUM CHLORIDE
CEFTAZIDIME SODIUM IN ISO-OSMOTIC DEXTROSE
CEFTAZIDIME/ARGININE
CEFTAZIDIME/AVIBACTAM SODIUM
CEFTIBUTEN
CEFTIZOXIME SODIUM
CEFTIZOXIME SODIUM/DEXTROSE, ISO-OSMOTIC
CEFTOLOZANE SULFATE/TAZOBACTAM SODIUM
CEFTRIAXONE SODIUM
CEFTRIAXONE SODIUM IN ISO-OSMOTIC DEXTROSE
CEFTRIAXONE SODIUM/LIDOCAINE HCL
CEFUROXIME AXETIL
CEFUROXIME SODIUM
CEFUROXIME SODIUM IN 0.9 % SODIUM CHLORIDE/PF
CEFUROXIME SODIUM/DEXTROSE 5 % IN WATER
CEFUROXIME SODIUM/DEXTROSE, ISO-OSMOTIC
CEFUROXIME SODIUM/WATER FOR INJECTION,STERILE
CHLORAMPHENICOL
CHLORAMPHENICOL PALMITATE
CHLORAMPHENICOL SOD SUCCINATE
CHLORAMPHENICOL/FIBRINOLYSIN/DESOXYRIBONUCLEASE
CHLOROALLYL METHENAMINE CHLORIDE
CHLORTETRACYCLINE HCL
CINOXACIN
CIPROFLOXACIN
CIPROFLOXACIN HCL
CIPROFLOXACIN HCL/DEXAMETHASONE
CIPROFLOXACIN HCL/FLUOCINOLONE ACETONIDE
CIPROFLOXACIN HCL/HYDROCORTISONE
CIPROFLOXACIN LACTATE
CIPROFLOXACIN LACTATE/DEXTROSE 5 % IN WATER

Appendix A

CIPROFLOXACIN/CIPROFLOXACIN HCL
CLARITHROMYCIN
CLINDAMYCIN HCL
CLINDAMYCIN PALMITATE HCL
CLINDAMYCIN PHOSPHATE
CLINDAMYCIN PHOSPHATE IN 0.9 % SODIUM CHLORIDE
CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE
CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE/EMOLLIENT COMB NO.94
CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE/HYALURONATE SODIUM
CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE/SKIN CLEANSER NO.5
CLINDAMYCIN PHOSPHATE/DEXTROSE 5 % IN WATER
CLINDAMYCIN PHOSPHATE/SKIN CLEANSER COMB NO.19
CLINDAMYCIN PHOSPHATE/TRETINOIN
CLOXACILLIN SODIUM
COLISTIN (AS COLISTIMETHATE SODIUM)
COLISTIN SULFATE
COLLOIDAL BISMUTH SUBCITRATE/METRONIDAZOLE/TETRACYCLINE HCL
DALBAVANCIN HCL
DAPTOMYCIN
DEMECLOCYCLINE HCL
DICLOXACILLIN SODIUM
DIRITHROMYCIN
DORIPENEM
DOXYCYCLINE CALCIUM
DOXYCYCLINE HYCLATE
DOXYCYCLINE HYCLATE/EYELID CLEANSER 3/EYELID EMOLLIENT NO.1
DOXYCYCLINE HYCLATE/EYELID CLEANSER NO2/EYELID CLEANSER NO3
DOXYCYCLINE HYCLATE/SKIN CLEANSER COMBINATION NO.19
DOXYCYCLINE MONOHYDRATE
DOXYCYCLINE MONOHYDRATE/BENZOYL PEROXIDE
DOXYCYCLINE MONOHYDRATE/OMEGA-3 COMBINATION NO.1/EYE MASK
DOXYCYCLINE MONOHYDRATE/SALICYLIC ACID/OCTINOXATE/ZINC OXIDE

Appendix A

DOXYCYCLINE MONOHYDRATE/SKIN CLEANSER COMBINATION NO.9
ENOXACIN
ERTAPENEM SODIUM
ERYTHROMYCIN BASE
ERYTHROMYCIN BASE IN ETHANOL
ERYTHROMYCIN BASE/BENZOYL PEROXIDE
ERYTHROMYCIN ESTOLATE
ERYTHROMYCIN ETHYLSUCCINATE
ERYTHROMYCIN ETHYLSUCCINATE/SULFISOXAZOLE ACETYL
ERYTHROMYCIN GLUCEPTATE
ERYTHROMYCIN LACTOBIONATE
ERYTHROMYCIN STEARATE
FOSFOMYCIN TROMETHAMINE
GATIFLOXACIN
GATIFLOXACIN/DEXTROSE 5 % IN WATER
GATIFLOXACIN/PREDNISOLONE ACETATE
GATIFLOXACIN/PREDNISOLONE ACETATE/BROMFENAC SODIUM
GATIFLOXACIN/PREDNISOLONE ACETATE/NEPAFENAC
GEMIFLOXACIN MESYLATE
GENTAMICIN SULFATE
GENTAMICIN SULFATE IN SODIUM CHLORIDE, ISO-OSMOTIC
GENTAMICIN SULFATE/PF
GENTAMICIN SULFATE/PREDNISOLONE ACETATE
GENTAMICIN SULFATE/SODIUM CHLORIDE
GENTAMICIN SULFATE/SODIUM CITRATE
GREPAFLOXACIN HCL
IMIPENEM/CILASTATIN SODIUM
KANAMYCIN SULFATE
LANSOPRAZOLE/AMOXICILLIN TRIHYDRATE/CLARITHROMYCIN
LEVOFLOXACIN
LEVOFLOXACIN/DEXTROSE 5 % IN WATER
LINCOMYCIN HCL

Appendix A

LINEZOLID
LINEZOLID IN 0.9 % SODIUM CHLORIDE
LINEZOLID IN DEXTROSE 5 % IN WATER
LOMEFLOXACIN HCL
LORACARBEF
MEROPENEM
MEROPENEM IN 0.9 % SODIUM CHLORIDE
MEROPENEM/VABORBACTAM
METHENAMINE
METHENAMINE HIPPURATE
METHENAMINE MANDELATE
METHENAMINE MANDELATE/SODIUM PHOSPHATE,MONOBASIC
METHENAMINE SULFOSALICYLATE/COAL TAR/MERCURY,AMMONIATED
METHENAMINE/BENZOIC ACID/SALICYLATE/SALICYLAMIDE
METHENAMINE/METHYLENE BLUE/BENZ AC/SALICYLATE/ATROP/HYOSCY
METHENAMINE/METHYLENE BLUE/BENZOIC ACID/SALICYLAT/HYOSCYAMIN
METHENAMINE/METHYLENE BLUE/BENZOIC/PHENYL SAL/ATROPIN/HYOSCY
METHENAMINE/METHYLENE BLUE/SALICYLATE/SODIUM PHOS/HYOSCYAMIN
METHENAMINE/METHYLENE BLUE/SALICYLATE/SODIUM/HYOSCYAMINE
METHENAMINE/METHYLENE BLUE/SOD PHOS/P.SALICYLATE/HYOSCYAMINE
METHENAMINE/SOD PHOSPH,MONOBASIC/METHYLENE BLUE/HYOSCYAMINE
METHENAMINE/SODIUM PHOSPHATE,MONOBASIC
METHENAMINE/SODIUM SALICYLATE
METRONIDAZOLE
METRONIDAZOLE BENZOATE
METRONIDAZOLE HCL
METRONIDAZOLE IN SODIUM CHLORIDE
METRONIDAZOLE/SKIN CLEANSER
METRONIDAZOLE/SKIN CLEANSER COMBINATION NO.23
MEZLOCILLIN SODIUM
MINOCYCLINE HCL
MINOCYCLINE HCL MICROSPHERES

Appendix A

MINOCYCLINE HCL/EMOL COMB NO.16/SKIN CLNSR L4/TOP AGENT NO.3
MINOCYCLINE HCL/EYELID CLEANSER COMBINATION NO. 1
MINOCYCLINE HCL/WIPES WITH SKIN CLEANSER NO.4
MOXIFLOXACIN HCL
MOXIFLOXACIN HCL IN BALANCE SALT IRRIGATION SOLUTION NO.2/PF
MOXIFLOXACIN HCL IN SODIUM ACETATE AND SULFATE,WATER,ISO-OSM
MOXIFLOXACIN HCL IN SODIUM CHLORIDE,ISO-OSMOTIC/PF
MOXIFLOXACIN HCL/DEXAMETHASONE SOD PH IN NACL,ISO-OSMOTIC/PF
MOXIFLOXACIN HCL/DEXAMETHASONE SOD PH/KETOROLAC/SOD CHL/PF
MOXIFLOXACIN HCL/SODIUM CHLORIDE, ISO-OSMOTIC
NAFCILLIN IN DEXTROSE, ISO-OSMOTIC
NAFCILLIN SODIUM
NAFCILLIN SODIUM/DEXTROSE 5 % IN WATER
NEOMYCIN SULF/BACITRACIN ZINC/POLYMYXIN B SULF/PRAMOXINE HCL
NEOMYCIN SULF/COLISTIN SUL/HYDROCORTISONE AC/THONZONIUM BROM
NEOMYCIN SULFATE
NEOMYCIN SULFATE/BACITRACIN ZINC/POLYMYXIN B
NEOMYCIN SULFATE/BACITRACIN ZINC/POLYMYXIN B SULFATE
NEOMYCIN SULFATE/BACITRACIN ZINC/POLYMYXIN B/HYDROCORTISONE
NEOMYCIN SULFATE/BACITRACIN ZINC/POLYMYXIN B/LIDOCAINE HCL
NEOMYCIN SULFATE/BACITRACIN/COLISTIMETHATE SODIUM
NEOMYCIN SULFATE/BACITRACIN/POLYMYXIN B
NEOMYCIN SULFATE/BACITRACIN/POLYMYXIN B/DIPERODON
NEOMYCIN SULFATE/BACITRACIN/POLYMYXIN B/LIDOCAINE
NEOMYCIN SULFATE/BACITRACIN/POLYMYXIN B/PRAMOXINE
NEOMYCIN SULFATE/COLISTIN SULFATE/HYDROCORTISONE
NEOMYCIN SULFATE/DEXAMETHASONE SODIUM PHOSPHATE
NEOMYCIN SULFATE/FLUOCINOLONE ACETONIDE
NEOMYCIN SULFATE/FLUOCINOLONE ACETONIDE/EMOLLIENT COMB NO.65
NEOMYCIN SULFATE/HYDROCORTISONE
NEOMYCIN SULFATE/HYDROCORTISONE ACETATE
NEOMYCIN SULFATE/POLYMYXIN B SULFATE

Appendix A

NEOMYCIN SULFATE/POLYMYXIN B SULFATE/BUFFERS/HYDROCORTISONE
NEOMYCIN SULFATE/POLYMYXIN B SULFATE/GRAMICIDIN D
NEOMYCIN SULFATE/POLYMYXIN B SULFATE/HYDROCORTISONE
NEOMYCIN SULFATE/POLYMYXIN B SULFATE/LIDOCAINE
NEOMYCIN SULFATE/POLYMYXIN B SULFATE/PRAMOXINE
NEOMYCIN SULFATE/POLYMYXIN B SULFATE/PREDNISOLONE
NEOMYCIN/BACITRACIN/POLYMYXIN B/HYDROCORTISONE
NEOMYCIN/POLYMYXIN B SULFATE/DEXAMETHASONE
NETILMICIN SULFATE
NITROFURANTOIN
NITROFURANTOIN MACROCRYSTAL
NITROFURANTOIN MONOHYDRATE/MACROCRYSTALS
NORFLOXACIN
OFLOXACIN
OFLOXACIN/DEXTROSE 5 % IN WATER
OMEPRAZOLE/CLARITHROMYCIN/AMOXICILLIN TRIHYDRATE
ORITAVANCIN DIPHOSPHATE
OXACILLIN SODIUM
OXACILLIN SODIUM IN ISO-OSMOTIC DEXTROSE
OXYTETRACYCLINE
OXYTETRACYCLINE HCL
OXYTETRACYCLINE HCL/HYDROCORTISONE ACETATE
OXYTETRACYCLINE HCL/POLYMYXIN B SULFATE
OXYTETRACYCLINE HCL/SULFAMETHIZOLE/PHENAZOPYRIDINE
OXYTETRACYCLINE/LIDOCAINE
PIPERACILLIN AND TAZOBACTAM IN DEXTROSE, ISO-OSMOTIC
PIPERACILLIN SODIUM
PIPERACILLIN SODIUM/DEXTROSE 5 % IN WATER
PIPERACILLIN SODIUM/TAZOBACTAM SODIUM
POLYMYXIN B SULFATE/TRIMETHOPRIM
QUINUPRISTIN/DALFOPRISTIN
SILVER SULFADIAZINE

Appendix A

SILVER SULFADIAZINE/FOAM BANDAGE
SPARFLOXACIN
SPECTINOMYCIN HCL
STREPTOMYCIN SULFATE
SUCCINYLSULFATHIAZOLE
SULFADIAZINE
SULFADIAZINE SODIUM
SULFAMERAZINE
SULFAMETHOXAZOLE
SULFAMETHOXAZOLE/PHENAZOPYRIDINE HCL
SULFAMETHOXAZOLE/TRIMETHOPRIM
SULFANILAMIDE
SULFAPYRIDINE
SULFATHIAZOLE
SULFATHIAZOLE SODIUM
SULFATHIAZOLE/SULFACETAMIDE/SULFABENZAMIDE
SULFATHIAZOLE/SULFACETAMIDE/SULFABENZAMIDE/UREA
TEDIZOLID PHOSPHATE
TELAVANCIN HCL
TELITHROMYCIN
TETRACYCLINE
TETRACYCLINE HCL
TICARCILLIN DISODIUM
TICARCILLIN DISODIUM/DEXTROSE 5 % IN WATER
TICARCILLIN DISODIUM/POTASSIUM CLAVULANATE
TINIDAZOLE
TOBRAMYCIN
TOBRAMYCIN IN 0.225 % SODIUM CHLORIDE
TOBRAMYCIN SULFATE
TOBRAMYCIN SULFATE/DEXTROSE 5 % IN WATER
TOBRAMYCIN SULFATE/SODIUM CHLORIDE
TOBRAMYCIN/DEXAMETHASONE

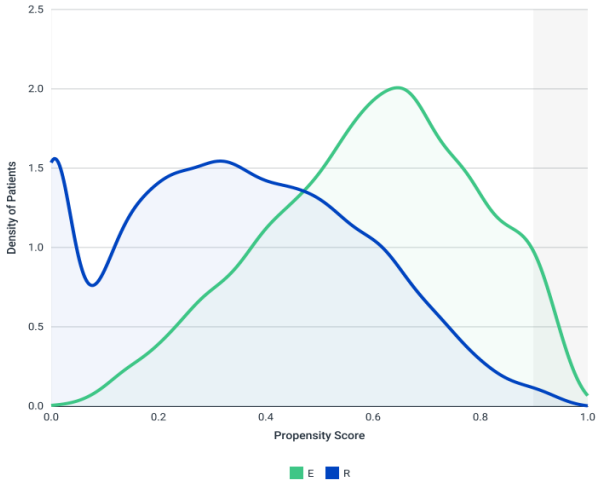
Appendix A

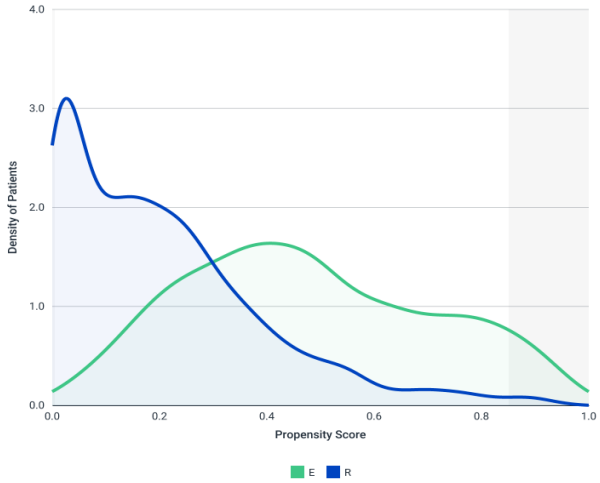
TOBRAMYCIN/LOTEPREDNOL ETABONATE
TOBRAMYCIN/NEBULIZER
TRIAMCINOLONE ACETONIDE/MOXIFLOXACIN HCL/WATER/PF
TRIMETHOPRIM
TRIMETHOPRIM, MICRONIZED
TROLEANDOMYCIN
TROVAFLOXACIN MESYLATE
VANCOMYCIN HCL
VANCOMYCIN HCL/BALANCED SALT SOLUTION NO.2/PF
VANCOMYCIN IN 0.9 % SODIUM CHLORIDE
VANCOMYCIN IN 5 % DEXTROSE IN WATER

Appendix B

Optum	MarketScan

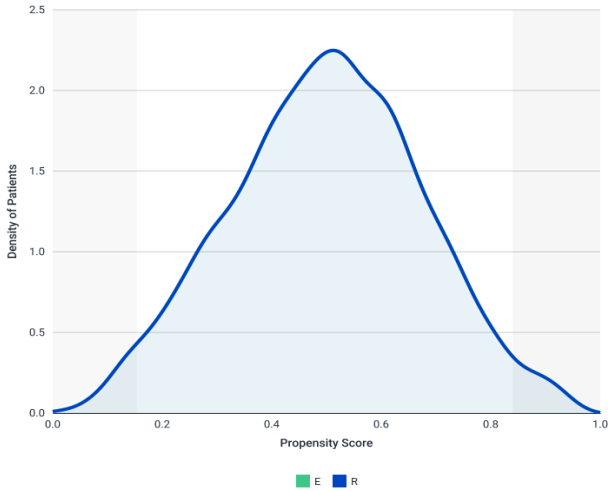
BEFORE PS MATCHING

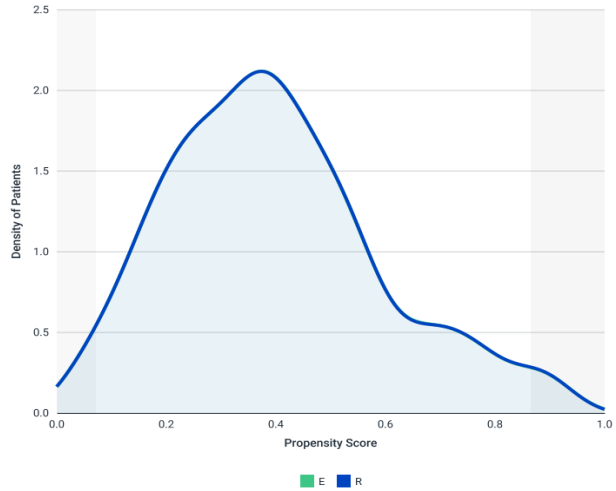




The c-statistics for the propensity score model, pre-matching was 0.786. The postmatching c-statistic was 0.527.	The c-statistics for the propensity score model, pre-matching was 0.829. The postmatching c-statistic was 0.577.

AFTER PS MATCHING





Appendix B

	Unmatched								
	Optum			Marketscan			POOLED		
Variable	**Breo ellipta (dual therapy)**	**Trelegy ellipta (triple therapy)**	**St. Diff.**	**Breo ellipta (dual therapy)**	**Trelegy ellipta (triple therapy)**	**St. Diff.**	**Breo ellipta (dual therapy)**	**Trelegy ellipta (triple therapy)**	**St. Diff.**
Number of patients	**7882**	**6796**		**1873**	**730**		**9,755**	**7,526**	
Year of Cohort Entry Date									
...2017; n (%)	968 (12.3%)	3 (0.0%)	0.050	489 (26.1%)	12 (1.6%)	0.066	1,457 (14.9%)	015 (0.2%)	0.579
...2018; n (%)	3,123 (39.6%)	1,451 (21.4%)	0.033	1,384 (73.9%)	718 (98.4%)	-0.027	4,507 (46.2%)	2,169 (28.8%)	0.365
...2019; n (%)	2,594 (32.9%)	3,507 (51.6%)	-0.029	NA	NA	NA	NA	NA	NA
...2020; n (%)	1,197 (15.2%)	1,835 (27.0%)	-0.026	NA	NA	NA	NA	NA	NA
Age									
...mean (sd)	69.65 (10.15)	70.22 (8.91)	-0.060	62.95 (11.21)	64.09 (9.74)	-0.109	68.36 (10.36)	69.63 (8.99)	-0.131
...median [IQR]	70.00 [63.00, 77.00]	71.00 [64.00, 77.00]	-0.105	61.00 [56.00, 70.00]	62.00 [58.00, 70.00]	-0.095	68.27 (10.36)	70.13 (8.99)	-0.192
Age categories									
...40-64; n (%)	2,264 (28.7%)	1,703 (25.1%)	0.007	1,245 (66.5%)	480 (65.8%)	0.001	3,509 (36.0%)	2,183 (29.0%)	0.150
...65 - 74; n (%)	3,005 (38.1%)	2,840 (41.8%)	-0.006	281 (15.0%)	121 (16.6%)	-0.004	3,286 (33.7%)	2,961 (39.3%)	-0.117
...>= 75; n (%)	2,613 (33.2%)	2,253 (33.2%)	0.000	347 (18.5%)	129 (17.7%)	0.002	2,960 (30.3%)	2,382 (31.7%)	-0.030
Geographic Region									
...Northeast; n (%)	828 (10.5%)	611 (9.0%)	0.005	383 (20.4%)	152 (20.8%)	-0.001	1,211 (12.4%)	763 (10.1%)	0.073
...North Central; n (%)	NA	NA	NA	457 (24.4%)	155 (21.2%)	0.007	NA	NA	NA
...South; n (%)	4,434 (56.3%)	3,910 (57.5%)	-0.002	874 (46.7%)	368 (50.4%)	-0.005	5,308 (54.4%)	4,278 (56.8%)	-0.048
...Midwest; n (%)	1,480 (18.8%)	1,260 (18.5%)	0.001	NA	NA	NA	NA	NA	NA
...West; n (%)	1,140 (14.5%)	1,015 (14.9%)	-0.001	158 (8.4%)	55 (7.5%)	0.003	1,298 (13.3%)	1,070 (14.2%)	-0.026
...Unknown/Missing; n (%)	NA	NA	NA	1 (0.1%)	0 (0.0%)	0.004	NA	NA	NA
General Health Related Measures									
Smoking; n (%)	3,293 (41.8%)	3,589 (52.8%)	-0.016	604 (32.2%)	353 (48.4%)	-0.026	3,897 (39.9%)	3,942 (52.4%)	-0.253
Alcohol/Drug abuse or dependence ; n (%)	474 (6.0%)	435 (6.4%)	-0.002	67 (3.6%)	28 (3.8%)	-0.001	541 (5.5%)	463 (6.2%)	-0.030
Obesity or Overweight; n (%)	2,608 (33.1%)	1,958 (28.8%)	0.008	480 (25.6%)	188 (25.8%)	0.000	3,088 (31.7%)	2,146 (28.5%)	0.070
Obesity; n (%)	1,952 (24.8%)	1,386 (20.4%)	0.009	384 (20.5%)	146 (20.0%)	0.001	2,336 (23.9%)	1,532 (20.4%)	0.084
Overweight; n (%)	806 (10.2%)	691 (10.2%)	0.000	115 (6.1%)	50 (6.8%)	-0.003	921 (9.4%)	741 (9.8%)	-0.014
Cardiovascular Measures									
Hypertension; n (%)	6,143 (77.9%)	5,080 (74.7%)	0.004	1,171 (62.5%)	467 (64.0%)	-0.002	7,314 (75.0%)	5,547 (73.7%)	0.030
Hyperlipidemia; n (%)	4,034 (51.2%)	3,358 (49.4%)	0.003	753 (40.2%)	281 (38.5%)	0.003	4,787 (49.1%)	3,639 (48.4%)	0.014
MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	1,926 (24.4%)	1,758 (25.9%)	-0.003	306 (16.3%)	151 (20.7%)	-0.010	2,232 (22.9%)	1,909 (25.4%)	-0.058
Old MI; n (%)	320 (4.1%)	244 (3.6%)	0.003	25 (1.3%)	9 (1.2%)	0.001	345 (3.5%)	253 (3.4%)	0.005
Acute MI; n (%)	0 (0.0%)	0 (0.0%)	-	10 (0.5%)	0 (0.0%)	0.010	010 (0.1%)	000 (0.0%)	0.045
Stable angina; n (%)	349 (4.4%)	310 (4.6%)	-0.001	58 (3.1%)	28 (3.8%)	-0.004	407 (4.2%)	338 (4.5%)	-0.015
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	1,773 (22.5%)	1,620 (23.8%)	-0.003	276 (14.7%)	139 (19.0%)	-0.010	2,049 (21.0%)	1,759 (23.4%)	-0.058
History of CABG or PTCA; n (%)	498 (6.3%)	424 (6.2%)	0.000	39 (2.1%)	19 (2.6%)	-0.003	537 (5.5%)	443 (5.9%)	-0.017
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)	379 (4.8%)	246 (3.6%)	0.006	75 (4.0%)	17 (2.3%)	0.010	454 (4.7%)	263 (3.5%)	0.061
Stroke (Ischemic or hemorrhagic); n (%)	222 (2.8%)	144 (2.1%)	0.004	44 (2.3%)	10 (1.4%)	0.007	266 (2.7%)	154 (2.0%)	0.046
TIA; n (%)	118 (1.5%)	85 (1.3%)	0.002	36 (1.9%)	6 (0.8%)	0.009	154 (1.6%)	091 (1.2%)	0.034
Late effects of cerebrovascular disease; n (%)	161 (2.0%)	76 (1.1%)	0.007	19 (1.0%)	3 (0.4%)	0.007	180 (1.8%)	079 (1.0%)	0.068
Atrial fibrillation and Other cardiac dysrhythmia; n (%)	1,380 (17.5%)	1,095 (16.1%)	0.003	223 (11.9%)	100 (13.7%)	-0.005	1,603 (16.4%)	1,195 (15.9%)	0.014
Atrial fibrillation; n (%)	930 (11.8%)	748 (11.0%)	0.002	140 (7.5%)	64 (8.8%)	-0.005	1,070 (11.0%)	812 (10.8%)	0.006
Other cardiac dysrhythmia; n (%)	1,380 (17.5%)	1,095 (16.1%)	0.003	223 (11.9%)	100 (13.7%)	-0.005	1,603 (16.4%)	1,195 (15.9%)	0.014
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)	2,383 (30.2%)	1,688 (24.8%)	0.010	393 (21.0%)	146 (20.0%)	0.002	2,776 (28.5%)	1,834 (24.4%)	0.093
Diabetes mellitus without mention of complications; n (%)	2,071 (26.3%)	1,462 (21.5%)	0.010	336 (17.9%)	131 (17.9%)	0.000	2,407 (24.7%)	1,593 (21.2%)	0.083
Diabetes with specified complications; n (%)	979 (12.4%)	617 (9.1%)	0.010	129 (6.9%)	41 (5.6%)	0.005	1,108 (11.4%)	658 (8.7%)	0.090
Diabetes with unspecified complications; n (%)	181 (2.3%)	144 (2.1%)	0.001	47 (2.5%)	11 (1.5%)	0.007	228 (2.3%)	155 (2.1%)	0.014
GI Conditions									
GERD; n (%)	2,251 (28.6%)	1,592 (23.4%)	0.010	396 (21.1%)	144 (19.7%)	0.003	2,647 (27.1%)	1,736 (23.1%)	0.092
Upper GI (Diseases of esophagus, stomach and duodenum including GERD) ; n (%)	2,432 (30.9%)	1,730 (25.5%)	0.010	451 (24.1%)	157 (21.5%)	0.005	2,883 (29.6%)	1,887 (25.1%)	0.101
GI bleeding; n (%)	236 (3.0%)	152 (2.2%)	0.005	40 (2.1%)	17 (2.3%)	-0.001	276 (2.8%)	169 (2.2%)	0.038
Non-infective enteritis and colitis; n (%)	221 (2.8%)	157 (2.3%)	0.003	46 (2.5%)	19 (2.6%)	-0.001	267 (2.7%)	176 (2.3%)	0.026

Appendix B

Intraoperative and postprocedural complications and disorders of digestive system; n (%)	183 (2.3%)	116 (1.7%)	0.004	30 (1.6%)	11 (1.5%)	0.001	213 (2.2%)	127 (1.7%)	0.036
Disorders of gallbladder, biliary tract and pancreas; n (%)	172 (2.2%)	145 (2.1%)	0.001	32 (1.7%)	14 (1.9%)	-0.001	204 (2.1%)	159 (2.1%)	0.000
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)	303 (3.8%)	213 (3.1%)	0.004	55 (2.9%)	21 (2.9%)	0.000	358 (3.7%)	234 (3.1%)	0.033
Osteoarthrosis; n (%)	2,153 (27.3%)	1,467 (21.6%)	0.012	319 (17.0%)	112 (15.3%)	0.004	2,472 (25.3%)	1,579 (21.0%)	0.102
Other rheumatic disorders (including gout); n (%)	3,412 (43.3%)	2,656 (39.1%)	0.007	600 (32.0%)	200 (27.4%)	0.008	4,012 (41.1%)	2,856 (37.9%)	0.065
Gout and other crystal arthropathies; n (%)	302 (3.8%)	211 (3.1%)	0.004	24 (1.3%)	6 (0.8%)	0.005	326 (3.3%)	217 (2.9%)	0.023
Other rheumatic disorders; n (%)	3,264 (41.4%)	2,539 (37.4%)	0.006	584 (31.2%)	198 (27.1%)	0.008	3,848 (39.4%)	2,737 (36.4%)	0.062
Neuro Conditions									
Alzheimer and other Dementia Disease ; n (%)	514 (6.5%)	245 (3.6%)	0.013	65 (3.5%)	8 (1.1%)	0.016	579 (5.9%)	253 (3.4%)	0.119
Seizure disorders (epilepsy); n (%)	183 (2.3%)	80 (1.2%)	0.008	16 (0.9%)	3 (0.4%)	0.006	199 (2.0%)	083 (1.1%)	0.073
Delirium/Psychosis; n (%)	340 (4.3%)	169 (2.5%)	0.010	48 (2.6%)	10 (1.4%)	0.008	388 (4.0%)	179 (2.4%)	0.091
Other Conditions									
Hypothyroidism; n (%)	1,566 (19.9%)	1,099 (16.2%)	0.009	267 (14.3%)	99 (13.6%)	0.002	1,833 (18.8%)	1,198 (15.9%)	0.077
Chronic kidney disease stages I-III; n (%)	1,352 (17.2%)	1,005 (14.8%)	0.006	118 (6.3%)	46 (6.3%)	0.000	1,470 (15.1%)	1,051 (14.0%)	0.031
Chronic kidney disease stages IV-V, ESRD; n (%)	195 (2.5%)	131 (1.9%)	0.004	24 (1.3%)	5 (0.7%)	0.006	219 (2.2%)	136 (1.8%)	0.029
COPD; n (%)	7,071 (89.7%)	6,609 (97.2%)	-0.008	1,603 (85.6%)	709 (97.1%)	-0.012	8,674 (88.9%)	7,318 (97.2%)	-0.331
Asthma; n (%)	2,558 (32.5%)	1,198 (17.6%)	0.030	710 (37.9%)	165 (22.6%)	0.028	3,268 (33.5%)	1,363 (18.1%)	0.358
Obstructive sleep apnea; n (%)	1,667 (21.1%)	1,427 (21.0%)	0.000	351 (18.7%)	164 (22.5%)	-0.008	2,018 (20.7%)	1,591 (21.1%)	-0.010
Syncope; n (%)	308 (3.9%)	172 (2.5%)	0.008	49 (2.6%)	16 (2.2%)	0.003	357 (3.7%)	188 (2.5%)	0.069
Falls; n (%)	571 (7.2%)	353 (5.2%)	0.008	55 (2.9%)	14 (1.9%)	0.006	626 (6.4%)	367 (4.9%)	0.065
VTE; n (%)	259 (3.3%)	184 (2.7%)	0.003	60 (3.2%)	9 (1.2%)	0.013	319 (3.3%)	193 (2.6%)	0.041
Combined comorbidity score, 365 days									
...mean (sd)	3.34 (2.76)	3.04 (2.53)	0.113	2.17 (2.14)	2.27 (2.07)	-0.047	3.12 (2.65)	2.97 (2.49)	0.058
...median [IQR]	3.00 [1.00, 5.00]	2.00 [1.00, 4.00]	0.378	1.00 [1.00, 3.00]	2.00 [1.00, 3.00]	-0.475	2.62 (2.65)	2.00 (2.49)	0.241
INDEX 2 - Frailty Score: Empirical Version 365 days as Categories, v3									
...< 0.1 non frail; n (%)	6,185 (78.5%)	4,989 (73.4%)	0.006	1,546 (82.5%)	534 (73.2%)	0.011	7,731 (79.3%)	5,523 (73.4%)	0.139
...0.1 - < 0.2 prefrail; n (%)	1,316 (16.7%)	1,598 (23.5%)	-0.015	246 (13.1%)	173 (23.7%)	-0.025	1,562 (16.0%)	1,771 (23.5%)	-0.189
... > 0.2 frail; n (%)	381 (4.8%)	209 (3.1%)	0.009	81 (4.3%)	23 (3.2%)	0.006	462 (4.7%)	232 (3.1%)	0.083
Medication Use									
Use of oral corticosteroids; n (%)	7,177 (91.1%)	6,374 (93.8%)	-0.003	1,774 (94.7%)	700 (95.9%)	-0.001	8,951 (91.8%)	7,074 (94.0%)	-0.086
Use of antidepressants; n (%)	3,422 (43.4%)	2,840 (41.8%)	0.002	755 (40.3%)	293 (40.1%)	0.000	4,177 (42.8%)	3,133 (41.6%)	0.024
Use of anticonvulsants; n (%)	2,188 (27.8%)	1,560 (23.0%)	0.010	383 (20.4%)	131 (17.9%)	0.006	2,571 (26.4%)	1,691 (22.5%)	0.091
Use of beta blocker OR calcium channel blocker; n (%)	3,181 (40.4%)	2,654 (39.1%)	0.002	583 (31.1%)	244 (33.4%)	-0.004	3,764 (38.6%)	2,898 (38.5%)	0.002
Use of PPIs; n (%)	2,956 (37.5%)	2,205 (32.4%)	0.009	611 (32.6%)	232 (31.8%)	0.001	3,567 (36.6%)	2,437 (32.4%)	0.088
Use of opioids; n (%)	2,762 (35.0%)	2,042 (30.0%)	0.009	587 (31.3%)	200 (27.4%)	0.007	3,349 (34.3%)	2,242 (29.8%)	0.097
Use of antipsychotics; n (%)	491 (6.2%)	339 (5.0%)	0.005	75 (4.0%)	35 (4.8%)	-0.004	566 (5.8%)	374 (5.0%)	0.035
Use of anxiolytics/hypnotics; n (%)	794 (10.1%)	651 (9.6%)	0.002	189 (10.1%)	78 (10.7%)	-0.002	983 (10.1%)	729 (9.7%)	0.013
Use of dementia meds; n (%)	290 (3.7%)	167 (2.5%)	0.007	37 (2.0%)	4 (0.5%)	0.013	327 (3.4%)	171 (2.3%)	0.066
Use of antiparkinsonian meds; n (%)	401 (5.1%)	306 (4.5%)	0.003	69 (3.7%)	26 (3.6%)	0.001	470 (4.8%)	332 (4.4%)	0.019
Use of Benzodiazepine; n (%)	1,723 (21.9%)	1,350 (19.9%)	0.004	346 (18.5%)	149 (20.4%)	-0.004	2,069 (21.2%)	1,499 (19.9%)	0.032
All antidiabetic medications; n (%)	1,859 (23.6%)	1,338 (19.7%)	0.008	336 (17.9%)	140 (19.2%)	-0.003	2,195 (22.5%)	1,478 (19.6%)	0.071
ACEI/ARB; n (%)	3,720 (47.2%)	3,158 (46.5%)	0.001	785 (41.9%)	309 (42.3%)	-0.001	4,505 (46.2%)	3,467 (46.1%)	0.002
Use of Anticoagulants; n (%)	879 (11.2%)	684 (10.1%)	0.003	150 (8.0%)	57 (7.8%)	0.001	1,029 (10.5%)	741 (9.8%)	0.023
Use of Amiodarone; n (%)	88 (1.1%)	76 (1.1%)	0.000	13 (0.7%)	9 (1.2%)	-0.005	101 (1.0%)	085 (1.1%)	-0.010
Digoxin; n (%)	97 (1.2%)	75 (1.1%)	0.001	16 (0.9%)	8 (1.1%)	-0.002	113 (1.2%)	083 (1.1%)	0.009
Use of Diuretics; n (%)	3,206 (40.7%)	2,565 (37.7%)	0.005	630 (33.6%)	268 (36.7%)	-0.005	3,836 (39.3%)	2,833 (37.6%)	0.035
Use of Aspirin; n (%)	39 (0.5%)	38 (0.6%)	-0.001	45 (2.4%)	15 (2.1%)	0.002	084 (0.9%)	053 (0.7%)	0.022
NSAIDs (NOT including aspirin); n (%)	1,489 (18.9%)	1,151 (16.9%)	0.005	379 (20.2%)	130 (17.8%)	0.006	1,868 (19.1%)	1,281 (17.0%)	0.055
HRT (Use of estrogens, progestins, androgens); n (%)	283 (3.6%)	216 (3.2%)	0.002	113 (6.0%)	42 (5.8%)	0.001	396 (4.1%)	258 (3.4%)	0.037
Use of Statins ; n (%)	4,228 (53.6%)	3,761 (55.3%)	-0.002	828 (44.2%)	317 (43.4%)	0.001	5,056 (51.8%)	4,078 (54.2%)	-0.048
Healthcare Utilization Measures									
Use of any drugs claims									
...mean (sd)	39.76 (25.49)	38.20 (22.20)	0.065	36.10 (22.86)	39.78 (22.55)	-0.162	39.06 (25.01)	38.35 (22.23)	0.030
...median [IQR]	35.00 [22.00, 52.00]	34.00 [22.00, 50.00]	0.042	32.00 [20.00, 48.00]	36.00 [23.00, 52.00]	-0.176	34.42 (25.01)	34.19 (22.23)	0.010
Number of office visits									
...mean (sd)	19.74 (13.91)	18.54 (12.12)	0.092	14.40 (10.08)	14.76 (9.75)	-0.036	18.71 (13.26)	18.17 (11.91)	0.043

Appendix B

...median [IQR]	17.00 [10.00, 26.00]	16.00 [10.00, 24.00]	0.077	12.00 [7.00, 19.00]	12.50 [8.00, 19.00]	-0.050	16.04 (13.26)	15.66 (11.91)	0.030
Number of ED visits									
...mean (sd)	1.41 (2.24)	1.08 (1.78)	0.163	1.23 (2.39)	0.99 (1.73)	0.115	1.38 (2.27)	1.07 (1.78)	0.152
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 1.00]	0.000	1.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.479	1.00 (2.27)	0.90 (1.78)	0.049
Number of hospitalizations									
...mean (sd)	0.27 (0.79)	0.16 (0.51)	0.165	1.12 (3.93)	0.81 (2.20)	0.097	0.43 (1.86)	0.22 (0.84)	0.146
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 (1.86)	0.00 (0.84)	0.000
Recent hospitalization (-30 days to Index Rx date); n (%)	253 (3.2%)	77 (1.1%)	0.014	51 (2.7%)	7 (1.0%)	0.013	304 (3.1%)	084 (1.1%)	0.140
Old hospitalizations (-365 to -31 days); n (%)	2,160 (27.4%)	1,723 (25.4%)	0.004	474 (25.3%)	196 (26.8%)	-0.003	2,634 (27.0%)	1,919 (25.5%)	0.034
Number of Pulmonologist visits									
...mean (sd)	0.09 (0.64)	0.10 (0.65)	-0.016	0.80 (1.38)	1.23 (1.60)	-0.288	0.23 (0.83)	0.21 (0.79)	0.025
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 [0.00, 1.00]	1.00 [0.00, 2.00]	-0.669	0.00 (0.83)	0.10 (0.79)	-0.123
Pulmonologist on CED ; n (%)	44 (0.6%)	50 (0.7%)	-0.001	207 (11.1%)	75 (10.3%)	0.002	251 (2.6%)	125 (1.7%)	0.062
Number of hospital days									
...mean (sd)	2.75 (10.57)	1.06 (5.13)	0.203	1.12 (3.93)	0.81 (2.20)	0.097	2.44 (9.66)	1.04 (4.92)	0.183
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 (9.66)	0.00 (4.92)	0.000
Occurrence of basic or comprehensive metabolic blood chemistry test; n (%)	5,479 (69.5%)	4,639 (68.3%)	0.001	811 (43.3%)	344 (47.1%)	-0.006	6,290 (64.5%)	4,983 (66.2%)	-0.036
Number of HbA1C test ordered									
...mean (sd)	1.17 (1.46)	1.05 (1.42)	0.083	0.66 (1.15)	0.59 (1.15)	0.061	1.07 (1.41)	1.01 (1.40)	0.043
...median [IQR]	1.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.694	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.000	0.81 (1.41)	0.00 (1.40)	0.577
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	353 (4.5%)	266 (3.9%)	0.003	88 (4.7%)	42 (5.8%)	-0.005	441 (4.5%)	308 (4.1%)	0.020
Number of Mammograms (Breast cancer screening); n (%)	1,076 (13.7%)	786 (11.6%)	0.006	220 (11.7%)	82 (11.2%)	0.001	1,296 (13.3%)	868 (11.5%)	0.055
Number of Pap smear (Cervical cancer screening); n (%)	216 (2.7%)	126 (1.9%)	0.005	85 (4.5%)	24 (3.3%)	0.006	301 (3.1%)	150 (2.0%)	0.070
Flu vaccine; n (%)	1,701 (21.6%)	1,389 (20.4%)	0.003	329 (17.6%)	114 (15.6%)	0.005	2,030 (20.8%)	1,503 (20.0%)	0.020
Pneumococcal vaccine; n (%)	2,199 (27.9%)	1,919 (28.2%)	-0.001	388 (20.7%)	143 (19.6%)	0.002	2,587 (26.5%)	2,062 (27.4%)	-0.020
Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	25.22 (31.21)	30.08 (33.34)	-0.150	19.06 (19.53)	22.29 (23.21)	-0.151	24.04 (29.33)	29.32 (32.50)	-0.171
...median [IQR]	17.78 [5.47, 34.48]	22.50 [7.34, 41.01]	-0.146	14.94 [6.77, 25.21]	18.31 [9.46, 28.28]	-0.157	17.23 (29.33)	22.09 (32.50)	-0.157
SES 9 Proxy - Business Type									
...Commercial; n (%)	1,247 (15.8%)	894 (13.2%)	0.007	NA	NA	NA	NA	NA	NA
...Medicare; n (%)	6,635 (84.2%)	5,902 (86.8%)	-0.003	NA	NA	NA	NA	NA	NA
SABA Copy; n (%)	4,493 (57.0%)	4,227 (62.2%)	-0.007	1,176 (62.8%)	514 (70.4%)	-0.009	5,669 (58.1%)	4,741 (63.0%)	-0.100
SAMA; n (%)	337 (4.3%)	309 (4.5%)	-0.001	72 (3.8%)	41 (5.6%)	-0.008	409 (4.2%)	350 (4.7%)	-0.024
SABA/SAMA Copy; n (%)	1,282 (16.3%)	1,384 (20.4%)	-0.010	276 (14.7%)	143 (19.6%)	-0.012	1,558 (16.0%)	1,527 (20.3%)	-0.112
ICS Copy; n (%)	1,736 (22.0%)	1,356 (20.0%)	0.004	443 (23.7%)	206 (28.2%)	-0.009	2,179 (22.3%)	1,562 (20.8%)	0.036
LABA Copy; n (%)	61 (0.8%)	73 (1.1%)	-0.003	17 (0.9%)	12 (1.6%)	-0.006	078 (0.8%)	085 (1.1%)	-0.031
LAMA Copy; n (%)	1,635 (20.7%)	1,458 (21.5%)	-0.002	513 (27.4%)	228 (31.2%)	-0.007	2,148 (22.0%)	1,686 (22.4%)	-0.010
LABA/ICS Combination Copy; n (%)	7,882 (100.0%)	2,193 (32.3%)	0.084	1,873 (100.0%)	319 (43.7%)	0.067	9,755 (100.0%)	2,512 (33.4%)	1.997
LAMA/LABA Combination Copy; n (%)	368 (4.7%)	1,228 (18.1%)	-0.040	88 (4.7%)	179 (24.5%)	-0.052	456 (4.7%)	1,407 (18.7%)	-0.446
LABA LAMA ICS Copy; n (%)	0 (0.0%)	6,796 (100.0%)	-0.142	0 (0.0%)	730 (100.0%)	-0.142	000 (0.0%)	7,526 (100.0%)	-
GOLD C/D status; n (%)	5,110 (64.8%)	5,219 (76.8%)	-0.014	1,067 (57.0%)	537 (73.6%)	-0.021	6,177 (63.3%)	5,756 (76.5%)	-0.291
blood eosinophilia test; n (%)	27 (0.3%)	23 (0.3%)	0.000	9 (0.5%)	3 (0.4%)	0.001	036 (0.4%)	026 (0.3%)	0.017
Serum immunoglobulin E (IgE) level test Copy; n (%)	204 (2.6%)	125 (1.8%)	0.005	60 (3.2%)	19 (2.6%)	0.004	264 (2.7%)	144 (1.9%)	0.053
H2 blocker; n (%)	686 (8.7%)	529 (7.8%)	0.003	130 (6.9%)	43 (5.9%)	0.004	816 (8.4%)	572 (7.6%)	0.029
Oxygen codes; n (%)	604 (7.7%)	945 (13.9%)	-0.019	115 (6.1%)	86 (11.8%)	-0.019	719 (7.4%)	1,031 (13.7%)	-0.206
Respiratory arrest/dependence on oxygen; n (%)	841 (10.7%)	1,085 (16.0%)	-0.015	166 (8.9%)	108 (14.8%)	-0.017	1,007 (10.3%)	1,193 (15.9%)	-0.167
Insurance Plan Type									
...Comprehensive; n (%)	NA	NA	NA	190 (10.1%)	98 (13.4%)	-0.010	NA	NA	NA
...HMO; n (%)	NA	NA	NA	195 (10.4%)	76 (10.4%)	0.000	NA	NA	NA
...PPO; n (%)	NA	NA	NA	1,021 (54.5%)	380 (52.1%)	0.003	NA	NA	NA
...Others; n (%)	NA	NA	NA	467 (24.9%)	176 (24.1%)	0.002	NA	NA	NA
Metropolitan Statistical Area									
...Urban; n (%)	NA	NA	NA	914 (48.8%)	372 (51.0%)	-0.003	NA	NA	NA
...Rural; n (%)	NA	NA	NA	343 (18.3%)	141 (19.3%)	-0.002	NA	NA	NA
...Unknown/Missing; n (%)	NA	NA	NA	616 (32.9%)	217 (29.7%)	0.006	NA	NA	NA

Aetion link to Optum results: https://bwh-dope.aetion.com/projects/details/1614/rwrs/69652
Aetion link to Marketscan results: https://bwh-dope.aetion.com/projects/details/1615/rwrs/69653

Appendix B

PS-matched									
	Optum			Marketscan			POOLED		
Variable	Breo ellipta (dual therapy)	Trelegy ellipta (triple therapy)	St. Diff.	Breo ellipta (dual therapy)	Trelegy ellipta (triple therapy)	St. Diff.	Breo ellipta (dual therapy)	Trelegy ellipta (triple therapy)	St. Diff.
Number of patients	**4248**	**4248**		**546**	**546**		**4,794**	**4,794**	
Year of Cohort Entry Date									
...2017; n (%)	3 (0.1%)	3 (0.1%)	0.0000	9 (1.6%)	12 (2.2%)	-0.0044	012 (0.3%)	015 (0.3%)	0.000
...2018; n (%)	1,216 (28.6%)	1,236 (29.1%)	-0.0009	537 (98.4%)	534 (97.8%)	0.0006	1138.67 (0.43)	1156.05 (0.43)	0.000
...2019; n (%)	2,039 (48.0%)	1,996 (47.0%)	0.0015	NA	NA	NA	NA	NA	NA
...2020; n (%)	990 (23.3%)	1,013 (23.8%)	-0.0010	NA	NA	NA	NA	NA	NA
Age*									
...mean (sd)	69.91 (9.75)	69.94 (9.22)	-0.0032	63.70 (10.74)	63.68 (9.77)	0.0019	69.20 (9.87)	69.23 (9.28)	-0.003
...median [IQR]	71.00 [64.00, 77.00]	71.00 [64.00, 76.00]	0.0000	62.00 [57.00, 70.00]	62.00 [57.00, 70.00]	0.0000	69.97 (9.87)	69.97 (9.28)	0.000
Age categories									
...40-64; n (%)	1,154 (27.2%)	1,129 (26.6%)	0.0012	357 (65.4%)	364 (66.7%)	-0.0016	1,511 (31.5%)	1,493 (31.1%)	0.009
...65 - 74; n (%)	1,682 (39.6%)	1,714 (40.3%)	-0.0011	87 (15.9%)	87 (15.9%)	0.0000	1,769 (36.9%)	1,801 (37.6%)	-0.014
...>= 75; n (%)	1,412 (33.2%)	1,405 (33.1%)	0.0002	102 (18.7%)	95 (17.4%)	0.0031	1,514 (31.6%)	1,500 (31.3%)	0.006
Geographic Region*									
...Northeast; n (%)	413 (9.7%)	404 (9.5%)	0.0006	114 (20.9%)	112 (20.5%)	0.0009	527 (11.0%)	516 (10.8%)	0.006
...North Central; n (%)	NA	NA	NA	122 (22.3%)	121 (22.2%)	0.0002	NA	NA	NA
...South; n (%)	2,444 (57.5%)	2,443 (57.5%)	0.0000	278 (50.9%)	273 (50.0%)	0.0013	2,722 (56.8%)	2,716 (56.7%)	0.002
...Midwest; n (%)	776 (18.3%)	792 (18.6%)	-0.0007	NA	NA	NA	NA	NA	NA
...West; n (%)	615 (14.5%)	609 (14.3%)	0.0005	32 (5.9%)	40 (7.3%)	-0.0055	647 (13.5%)	649 (13.5%)	0.000
...Unknown/Missing; n (%)	NA	NA	NA	0 (0.0%)	0 (0.0%)	-	NA	NA	NA
General Health Related Measures									
Smoking; n (%)*	1,987 (46.8%)	2,011 (47.3%)	-0.0007	254 (46.5%)	245 (44.9%)	0.0024	2,241 (46.7%)	2,256 (47.1%)	-0.008
Alcohol/Drug abuse or dependence ; n (%)	264 (6.2%)	261 (6.1%)	0.0004	21 (3.8%)	21 (3.8%)	0.0000	285 (5.9%)	282 (5.9%)	0.000
Obesity or Overweight; n (%)*	1,287 (30.3%)	1,323 (31.1%)	-0.0014	132 (24.2%)	146 (26.7%)	-0.0050	1,419 (29.6%)	1,469 (30.6%)	-0.022
Obesity; n (%)	947 (22.3%)	945 (22.2%)	0.0002	105 (19.2%)	117 (21.4%)	-0.0049	1,052 (21.9%)	1,062 (22.2%)	-0.007
Overweight; n (%)	411 (9.7%)	456 (10.7%)	-0.0031	35 (6.4%)	36 (6.6%)	-0.0008	446 (9.3%)	492 (10.3%)	-0.034
Cardiovascular Measures									
Hypertension; n (%)*	3,229 (76.0%)	3,262 (76.8%)	-0.0009	336 (61.5%)	342 (62.6%)	-0.0014	3,565 (74.4%)	3,604 (75.2%)	-0.018
Hyperlipidemia; n (%)*	2,122 (50.0%)	2,114 (49.8%)	0.0003	203 (37.2%)	208 (38.1%)	-0.0015	2,325 (48.5%)	2,322 (48.4%)	0.002
MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)*	1,047 (24.6%)	1,043 (24.6%)	0.0000	97 (17.8%)	106 (19.4%)	-0.0037	1,144 (23.9%)	1,149 (24.0%)	-0.002
Old MI; n (%)	166 (3.9%)	155 (3.6%)	0.0015	9 (1.6%)	5 (0.9%)	0.0063	175 (3.7%)	160 (3.3%)	0.022
Acute MI; n (%)	0 (0.0%)	0 (0.0%)	-	3 (0.5%)	0 (0.0%)	0.0100	003 (0.1%)	000 (0.0%)	0.045
Stable angina; n (%)	193 (4.5%)	187 (4.4%)	0.0005	21 (3.8%)	23 (4.2%)	-0.0020	214 (4.5%)	210 (4.4%)	0.005
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	971 (22.9%)	958 (22.6%)	0.0006	89 (16.3%)	96 (17.6%)	-0.0032	1,060 (22.1%)	1,054 (22.0%)	0.002
History of CABG or PTCA; n (%)	268 (6.3%)	260 (6.1%)	0.0008	12 (2.2%)	14 (2.6%)	-0.0026	280 (5.8%)	274 (5.7%)	0.004
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)*	166 (3.9%)	169 (4.0%)	-0.0005	11 (2.0%)	15 (2.7%)	-0.0046	177 (3.7%)	184 (3.8%)	-0.005
Stroke (Ischemic or hemorrhagic); n (%)	88 (2.1%)	101 (2.4%)	-0.0020	7 (1.3%)	9 (1.6%)	-0.0025	095 (2.0%)	110 (2.3%)	-0.021
TIA; n (%)	61 (1.4%)	58 (1.4%)	0.0000	6 (1.1%)	6 (1.1%)	0.0000	067 (1.4%)	064 (1.3%)	0.009
Late effects of cerebrovascular disease; n (%)	60 (1.4%)	59 (1.4%)	0.0000	0 (0.0%)	2 (0.4%)	-0.0089	060 (1.3%)	061 (1.3%)	0.000
Atrial fibrillation and Other cardiac dysrhythmia; n (%)*	707 (16.6%)	688 (16.2%)	0.0010	67 (12.3%)	72 (13.2%)	-0.0025	774 (16.1%)	760 (15.9%)	0.005
Atrial fibrillation; n (%)	467 (11.0%)	474 (11.2%)	-0.0006	47 (8.6%)	43 (7.9%)	0.0024	514 (10.7%)	517 (10.8%)	-0.003
Other cardiac dysrhythmia; n (%)	707 (16.6%)	688 (16.2%)	0.0010	67 (12.3%)	72 (13.2%)	-0.0025	774 (16.1%)	760 (15.9%)	0.005
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)*	1,151 (27.1%)	1,149 (27.0%)	0.0002	106 (19.4%)	110 (20.1%)	-0.0016	1,257 (26.2%)	1,259 (26.3%)	-0.002
Diabetes mellitus without mention of complications; n (%)	969 (22.8%)	989 (23.3%)	-0.0010	94 (17.2%)	96 (17.6%)	-0.0010	1,063 (22.2%)	1,085 (22.6%)	-0.010
Diabetes with specified complications; n (%)	471 (11.1%)	441 (10.4%)	0.0021	38 (7.0%)	33 (6.0%)	0.0039	509 (10.6%)	474 (9.9%)	0.023
Diabetes with unspecified complications; n (%)	84 (2.0%)	102 (2.4%)	-0.0027	17 (3.1%)	7 (1.3%)	0.0121	101 (2.1%)	109 (2.3%)	-0.014
GI Conditions									
GERD; n (%)*	1,067 (25.1%)	1,068 (25.1%)	0.0000	98 (17.9%)	108 (19.8%)	-0.0044	1,165 (24.3%)	1,176 (24.5%)	-0.005
Upper GI (Diseases of esophagus, stomach and duodenum including GERD) ; n (%)	1,149 (27.0%)	1,166 (27.4%)	-0.0008	118 (21.6%)	117 (21.4%)	0.0004	1,267 (26.4%)	1,283 (26.8%)	-0.009
GI bleeding; n (%)*	100 (2.4%)	104 (2.4%)	0.0000	14 (2.6%)	14 (2.6%)	0.0000	114 (2.4%)	118 (2.5%)	-0.006
Non-infective enteritis and colitis; n (%)	110 (2.6%)	103 (2.4%)	0.0013	12 (2.2%)	13 (2.4%)	-0.0013	122 (2.5%)	116 (2.4%)	0.006

Appendix B

Intraoperative and postprocedural complications and disorders of digestive system; n (%)	82 (1.9%)	73 (1.7%)	0.0015	9 (1.6%)	9 (1.6%)	0.0000	091 (1.9%)	082 (1.7%)	0.015
Disorders of gallbladder, biliary tract and pancreas; n (%)*	92 (2.2%)	89 (2.1%)	0.0007	11 (2.0%)	12 (2.2%)	-0.0014	103 (2.1%)	101 (2.1%)	0.000
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)*	142 (3.3%)	148 (3.5%)	-0.0011	16 (2.9%)	14 (2.6%)	0.0018	158 (3.3%)	162 (3.4%)	-0.006
Osteoarthrosis; n (%)*	1,006 (23.7%)	1,014 (23.9%)	-0.0004	85 (15.6%)	82 (15.0%)	0.0015	1,091 (22.8%)	1,096 (22.9%)	-0.002
Other rheumatic disorders (including gout); n (%)*	1,738 (40.9%)	1,755 (41.3%)	-0.0006	155 (28.4%)	161 (29.5%)	-0.0020	1,893 (39.5%)	1,916 (40.0%)	-0.010
Gout and other crystal arthropathies; n (%)	147 (3.5%)	142 (3.3%)	0.0011	7 (1.3%)	6 (1.1%)	0.0018	154 (3.2%)	148 (3.1%)	0.006
Other rheumatic disorders; n (%)	1,666 (39.2%)	1,676 (39.5%)	-0.0005	150 (27.5%)	159 (29.1%)	-0.0030	1,816 (37.9%)	1,835 (38.3%)	-0.008
Neuro Conditions									
Alzheimer and other Dementia Disease ; n (%)*	191 (4.5%)	185 (4.4%)	0.0005	8 (1.5%)	7 (1.3%)	0.0017	199 (4.2%)	192 (4.0%)	0.010
Seizure disorders (epilepsy); n (%)*	69 (1.6%)	64 (1.5%)	0.0008	0 (0.0%)	2 (0.4%)	-0.0089	069 (1.4%)	066 (1.4%)	0.000
Delirium/Psychosis; n (%)*	118 (2.8%)	116 (2.7%)	0.0006	9 (1.6%)	5 (0.9%)	0.0063	127 (2.6%)	121 (2.5%)	0.006
Other Conditions									
Hypothyroidism; n (%)*	748 (17.6%)	744 (17.5%)	0.0002	84 (15.4%)	76 (13.9%)	0.0039	832 (17.4%)	820 (17.1%)	0.008
Chronic kidney disease stages I-III; n (%)*	646 (15.2%)	663 (15.6%)	-0.0010	31 (5.7%)	33 (6.0%)	-0.0012	677 (14.1%)	696 (14.5%)	-0.011
Chronic kidney disease stages IV-V, ESRD; n (%)	87 (2.0%)	86 (2.0%)	0.0000	7 (1.3%)	4 (0.7%)	0.0060	094 (2.0%)	090 (1.9%)	0.007
COPD; n (%)	3,860 (90.9%)	4,087 (96.2%)	-0.0055	503 (92.1%)	527 (96.5%)	-0.0046	4,363 (91.0%)	4,614 (96.2%)	-0.214
Asthma; n (%)*	988 (23.3%)	1,018 (24.0%)	-0.0014	149 (27.3%)	140 (25.6%)	0.0033	1,137 (23.7%)	1,158 (24.2%)	-0.012
Obstructive sleep apnea; n (%)*	870 (20.5%)	890 (21.0%)	-0.0011	104 (19.0%)	118 (21.6%)	-0.0058	974 (20.3%)	1,008 (21.0%)	-0.017
Syncope; n (%)	134 (3.2%)	120 (2.8%)	0.0023	14 (2.6%)	9 (1.6%)	0.0069	148 (3.1%)	129 (2.7%)	0.024
Falls; n (%)	227 (5.3%)	237 (5.6%)	-0.0013	10 (1.8%)	12 (2.2%)	-0.0028	237 (4.9%)	249 (5.2%)	-0.014
VTE; n (%)*	119 (2.8%)	121 (2.8%)	0.0000	9 (1.6%)	8 (1.5%)	0.0008	128 (2.7%)	129 (2.7%)	0.000
Combined comorbidity score, 365 days*									
...mean (sd)	3.14 (2.58)	3.14 (2.63)	0.0000	2.22 (2.09)	2.27 (2.07)	-0.0240	3.04 (2.53)	3.04 (2.57)	0.000
...median [IQR]	3.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.3839	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]	0.0000	2.89 (2.53)	2.00 (2.57)	0.349
INDEX 2 - Frailty Score: Empirical Version 365 days as Categories, v3*									
...< 0.1 non frail; n (%)	3,304 (77.8%)	3,296 (77.6%)	0.0002	417 (76.4%)	418 (76.6%)	-0.0002	3,721 (77.6%)	3,714 (77.5%)	0.002
...0.1 - < 0.2 prefrail; n (%)	786 (18.5%)	801 (18.9%)	-0.0009	111 (20.3%)	108 (19.8%)	0.0011	897 (18.7%)	909 (19.0%)	-0.008
... > 0.2 frail; n (%)	158 (3.7%)	151 (3.6%)	0.0005	18 (3.3%)	20 (3.7%)	-0.0021	176 (3.7%)	171 (3.6%)	0.005
Medication Use									
Use of oral corticosteroids; n (%)*	3,931 (92.5%)	3,936 (92.7%)	-0.0002	528 (96.7%)	522 (95.6%)	0.0011	4,459 (93.0%)	4,458 (93.0%)	0.000
Use of antidepressants; n (%)*	1,804 (42.5%)	1,817 (42.8%)	-0.0005	226 (41.4%)	221 (40.5%)	0.0014	2,030 (42.3%)	2,038 (42.5%)	-0.004
Use of anticonvulsants; n (%)*	1,070 (25.2%)	1,083 (25.5%)	-0.0006	97 (17.8%)	97 (17.8%)	0.0000	1,167 (24.3%)	1,180 (24.6%)	-0.007
Use of beta blocker OR calcium channel blocker; n (%)*	1,672 (39.4%)	1,679 (39.5%)	-0.0002	177 (32.4%)	174 (31.9%)	0.0009	1,849 (38.6%)	1,853 (38.7%)	-0.002
Use of PPIs; n (%)*	1,461 (34.4%)	1,498 (35.3%)	-0.0015	174 (31.9%)	178 (32.6%)	-0.0012	1,635 (34.1%)	1,676 (35.0%)	-0.019
Use of opioids; n (%)*	1,358 (32.0%)	1,360 (32.0%)	0.0000	149 (27.3%)	150 (27.5%)	-0.0004	1,507 (31.4%)	1,510 (31.5%)	-0.002
Use of antipsychotics; n (%)*	221 (5.2%)	222 (5.2%)	0.0000	25 (4.6%)	25 (4.6%)	0.0000	246 (5.1%)	247 (5.2%)	-0.005
Use of anxiolytics/hypnotics; n (%)*	416 (9.8%)	420 (9.9%)	-0.0003	55 (10.1%)	56 (10.3%)	-0.0006	471 (9.8%)	476 (9.9%)	-0.003
Use of dementia meds; n (%)*	122 (2.9%)	134 (3.2%)	-0.0017	5 (0.9%)	4 (0.7%)	0.0022	127 (2.6%)	138 (2.9%)	-0.018
Use of antiparkinsonian meds; n (%)*	204 (4.8%)	194 (4.6%)	0.0009	22 (4.0%)	18 (3.3%)	0.0037	226 (4.7%)	212 (4.4%)	0.014
Use of Benzodiazepine; n (%)*	850 (20.0%)	854 (20.1%)	-0.0002	111 (20.3%)	110 (20.1%)	0.0004	961 (20.0%)	964 (20.1%)	-0.002
All antidiabetic medications; n (%)*	901 (21.2%)	907 (21.4%)	-0.0004	99 (18.1%)	107 (19.6%)	-0.0035	1,000 (20.9%)	1,014 (21.2%)	-0.007
ACEI/ARB; n (%)*	2,013 (47.4%)	2,018 (47.5%)	-0.0001	225 (41.2%)	231 (42.3%)	-0.0017	2,238 (46.7%)	2,249 (46.9%)	-0.004
Use of Anticoagulants; n (%)*	446 (10.5%)	449 (10.6%)	-0.0003	48 (8.8%)	50 (9.2%)	-0.0013	494 (10.3%)	499 (10.4%)	-0.003
Use of Amiodarone; n (%)	46 (1.1%)	54 (1.3%)	-0.0018	4 (0.7%)	6 (1.1%)	-0.0042	050 (1.0%)	060 (1.3%)	-0.028
Digoxin; n (%)	51 (1.2%)	51 (1.2%)	0.0000	3 (0.5%)	6 (1.1%)	-0.0067	054 (1.1%)	057 (1.2%)	-0.009
Use of Diuretics; n (%)*	1,653 (38.9%)	1,668 (39.3%)	-0.0006	193 (35.3%)	192 (35.2%)	0.0002	1,846 (38.5%)	1,860 (38.8%)	-0.006
Use of Aspirin; n (%)	19 (0.4%)	30 (0.7%)	-0.0040	12 (2.2%)	12 (2.2%)	0.0000	031 (0.6%)	042 (0.9%)	-0.035
NSAIDs (NOT including aspirin); n (%)	742 (17.5%)	741 (17.4%)	0.0002	112 (20.5%)	95 (17.4%)	0.0071	854 (17.8%)	836 (17.4%)	0.011
HRT (Use of estrogens, progestins, androgens); n (%)*	142 (3.3%)	142 (3.3%)	0.0000	28 (5.1%)	36 (6.6%)	-0.0062	170 (3.5%)	178 (3.7%)	-0.011
Use of Statins ; n (%)*	2,335 (55.0%)	2,355 (55.4%)	-0.0005	244 (44.7%)	234 (42.9%)	0.0027	2,579 (53.8%)	2,589 (54.0%)	-0.004
Healthcare Utilization Measures									
Use of any drugs claims*									
...mean (sd)	38.70 (25.02)	38.49 (22.66)	0.0088	38.41 (24.47)	38.81 (22.54)	-0.0170	38.67 (24.96)	38.53 (22.65)	0.006
...median [IQR]	34.00 [21.00, 51.00]	34.00 [22.00, 50.00]	0.0000	34.50 [21.00, 50.25]	35.00 [23.00, 50.00]	-0.0213	34.06 (24.96)	34.11 (22.65)	-0.002
Number of office visits*									
...mean (sd)	18.87 (12.67)	18.79 (12.49)	0.0064	14.24 (9.91)	14.60 (9.82)	-0.0365	18.34 (12.39)	18.31 (12.22)	0.002

Appendix B

...median [IQR]	16.00 [10.00, 24.75]	16.00 [10.00, 24.00]	0.0000	12.00 [7.00, 18.00]	12.00 [8.00, 19.00]	0.0000	15.54 (12.39)	15.54 (12.22)	0.000
Number of ED visits*									
...mean (sd)	1.19 (1.76)	1.19 (1.95)	0.0000	0.99 (1.47)	1.02 (1.70)	-0.0189	1.17 (1.73)	1.17 (1.92)	0.000
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.0000	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.0000	0.89 (1.73)	0.89 (1.92)	0.000
Number of hospitalizations*									
...mean (sd)	0.17 (0.52)	0.18 (0.57)	-0.0183	0.89 (2.85)	0.86 (2.33)	0.0115	0.25 (1.08)	0.26 (0.95)	-0.010
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (1.08)	0.00 (0.95)	0.000
Recent hospitalization (-30 days to Index Rx date); n (%)*	71 (1.7%)	66 (1.6%)	0.0008	8 (1.5%)	6 (1.1%)	0.0035	079 (1.6%)	072 (1.5%)	0.008
Old hospitalizations (-365 to -31 days); n (%)*	1,070 (25.2%)	1,098 (25.8%)	-0.0012	144 (26.4%)	146 (26.7%)	-0.0006	1,214 (25.3%)	1,244 (25.9%)	-0.014
Number of Pulmonologist visits*									
...mean (sd)	0.09 (0.67)	0.09 (0.61)	0.0000	1.08 (1.76)	1.15 (1.49)	-0.0429	0.20 (0.87)	0.21 (0.76)	-0.012
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 2.00]	1.00 [0.00, 2.00]	-0.6133	0.00 (0.87)	0.11 (0.76)	-0.135
Pulmonologist on CED ; n (%)*	24 (0.6%)	23 (0.5%)	0.0013	55 (10.1%)	61 (11.2%)	-0.0034	079 (1.6%)	084 (1.8%)	-0.015
Number of hospital days*									
...mean (sd)	1.25 (5.14)	1.29 (6.09)	-0.0071	0.89 (2.85)	0.86 (2.33)	0.0115	1.21 (4.93)	1.24 (5.79)	-0.006
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.0000	0.00 (4.93)	0.00 (5.79)	0.000
Occurrence of basic or comprehensive metabolic blood chemistry test; n (%)*	2,888 (68.0%)	2,903 (68.3%)	-0.0004	256 (46.9%)	252 (46.2%)	0.0010	3,144 (65.6%)	3,155 (65.8%)	-0.004
Number of HbA1C test ordered*									
...mean (sd)	1.11 (1.45)	1.11 (1.46)	0.0000	0.58 (1.08)	0.61 (1.18)	-0.0265	1.05 (1.41)	1.05 (1.43)	0.000
...median [IQR]	1.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.6873	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.89 (1.41)	0.00 (1.43)	0.627
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)*	171 (4.0%)	169 (4.0%)	0.0000	27 (4.9%)	32 (5.9%)	-0.0043	198 (4.1%)	201 (4.2%)	-0.005
Number of Mammograms (Breast cancer screening); n (%)*	534 (12.6%)	529 (12.5%)	0.0003	62 (11.4%)	64 (11.7%)	-0.0009	596 (12.4%)	593 (12.4%)	0.000
Number of Pap smear (Cervical cancer screening); n (%)*	86 (2.0%)	97 (2.3%)	-0.0020	18 (3.3%)	20 (3.7%)	-0.0021	104 (2.2%)	117 (2.4%)	-0.013
Flu vaccine; n (%)*	865 (20.4%)	852 (20.1%)	0.0007	85 (15.6%)	90 (16.5%)	-0.0022	950 (19.8%)	942 (19.6%)	0.005
Pneumococcal vaccine; n (%)*	1,184 (27.9%)	1,149 (27.0%)	0.0017	107 (19.6%)	114 (20.9%)	-0.0029	1,291 (26.9%)	1,263 (26.3%)	0.014
Copay for pharmacy cost (charges in U.S. $)*									
...mean (sd)	27.30 (35.49)	27.85 (31.85)	-0.0163	21.53 (22.71)	20.69 (20.10)	0.0392	26.64 (34.28)	27.03 (30.74)	-0.012
...median [IQR]	19.37 [6.01, 36.26]	20.58 [6.59, 38.83]	-0.0359	16.99 [7.47, 28.40]	17.25 [9.01, 26.47]	-0.0121	19.10 (34.28)	20.20 (30.74)	-0.034
SES 9 Proxy - Business Type*									
...Commercial; n (%)	605 (14.2%)	586 (13.8%)	0.0011	NA	NA	NA	NA	NA	NA
...Medicare; n (%)	3,643 (85.8%)	3,662 (86.2%)	-0.0004	NA	NA	NA	NA	NA	NA
SABA Copy; n (%)*	2,502 (58.9%)	2,495 (58.7%)	0.0003	387 (70.9%)	377 (69.0%)	0.0023	2,889 (60.3%)	2,872 (59.9%)	0.008
SAMA; n (%)*	176 (4.1%)	189 (4.4%)	-0.0015	32 (5.9%)	28 (5.1%)	0.0034	208 (4.3%)	217 (4.5%)	-0.010
SABA/SAMA Copy; n (%)*	757 (17.8%)	763 (18.0%)	-0.0005	113 (20.7%)	105 (19.2%)	0.0034	870 (18.1%)	868 (18.1%)	0.000
ICS Copy; n (%)*	856 (20.2%)	870 (20.5%)	-0.0007	142 (26.0%)	150 (27.5%)	-0.0029	998 (20.8%)	1,020 (21.3%)	-0.012
LABA Copy; n (%)*	37 (0.9%)	40 (0.9%)	0.0000	5 (0.9%)	8 (1.5%)	-0.0055	042 (0.9%)	048 (1.0%)	-0.010
LAMA Copy; n (%)*	918 (21.6%)	926 (21.8%)	-0.0004	189 (34.6%)	177 (32.4%)	0.0038	1,107 (23.1%)	1,103 (23.0%)	0.002
LABA/ICS Combination Copy; n (%)	4,248 (100.0%)	1,462 (34.4%)	0.0804	546 (100.0%)	254 (46.5%)	0.0628	4,794 (100.0%)	1,716 (35.8%)	1.894
LAMA/LABA Combination Copy; n (%)*	301 (7.1%)	312 (7.3%)	-0.0007	65 (11.9%)	73 (13.4%)	-0.0042	366 (7.6%)	385 (8.0%)	-0.015
LABA LAMA ICS Copy; n (%)	0 (0.0%)	4,248 (100.0%)	-0.1421	0 (0.0%)	546 (100.0%)	-0.1421	000 (0.0%)	4,794 (100.0%)	-
GOLD C/D status; n (%)*	3,022 (71.1%)	3,021 (71.1%)	0.0000	387 (70.9%)	378 (69.2%)	0.0020	3,409 (71.1%)	3,399 (70.9%)	0.004
blood eosinophilia test; n (%)*	14 (0.3%)	15 (0.4%)	-0.0017	3 (0.5%)	3 (0.5%)	0.0000	017 (0.4%)	018 (0.4%)	0.000
Serum immunoglobulin E (IgE) level test Copy; n (%)*	100 (2.4%)	94 (2.2%)	0.0013	13 (2.4%)	15 (2.7%)	-0.0019	113 (2.4%)	109 (2.3%)	0.007
H2 blocker; n (%)*	340 (8.0%)	336 (7.9%)	0.0004	30 (5.5%)	31 (5.7%)	-0.0008	370 (7.7%)	367 (7.7%)	0.000
Oxygen codes; n (%)*	396 (9.3%)	413 (9.7%)	-0.0013	61 (11.2%)	61 (11.2%)	0.0000	457 (9.5%)	474 (9.9%)	-0.014
Respiratory arrest/dependence on oxygen; n (%)*	501 (11.8%)	516 (12.1%)	-0.0009	70 (12.8%)	69 (12.6%)	0.0006	571 (11.9%)	585 (12.2%)	-0.009
Insurance Plan Type*									
...Comprehensive; n (%)	NA	NA	NA	63 (11.5%)	68 (12.5%)	-0.0029	NA	NA	NA
...HMO; n (%)	NA	NA	NA	54 (9.9%)	55 (10.1%)	-0.0006	NA	NA	NA
...PPO; n (%)	NA	NA	NA	287 (52.6%)	289 (52.9%)	-0.0004	NA	NA	NA
...Others; n (%)	NA	NA	NA	142 (26.0%)	134 (24.5%)	0.0030	NA	NA	NA
Metropolitan Statistical Area*									
...Urban; n (%)	NA	NA	NA	286 (52.4%)	278 (50.9%)	0.0021	NA	NA	NA
...Rural; n (%)	NA	NA	NA	108 (19.8%)	101 (18.5%)	0.0030	NA	NA	NA
...Unknown/Missing; n (%)	NA	NA	NA	152 (27.8%)	167 (30.6%)	-0.0052	NA	NA	NA

***Included in the 1:1 PS matching model**