Replication of the P04334 Asthma Trial in Healthcare Claims Data

DUPLICATE-P04334

September 14, 2021

NCT04892758

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

Effects of Mometasone Furoate/Formoterol Combination Versus Mometasone Furoate Alone Versus Formoterol alone in Persistent Asthmatics (Study P04334AM1; NCT00383240)

1.2 Intended aim(s)

To assess the effects of 26 weeks of treatment with mometasone furoate/formoterol (MF/F) compared with formoterol (F) alone on the incidence of time to first asthma deterioration in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids.

1.3 Primary endpoint for replication

Asthma exacerbation defined by hospitalization or treatment with additional excluded asthma medication (i.e., systemic corticosteroids)

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

This trial is a superiority trial. For time to first asthma deterioration, assuming a 5% event rate for MF/F 200/10 ug and an 18% event rate for F 10 ug, the trial's sample size will provide ~90% power to detect a treatment difference in survival curves.

1.5 Trial estimate

The proportion of patients experiencing asthma deteriorations was MF/F, 30.4%, MF, 33.9%, F 54% ($p < 0.001$). (Nathan et al., 2010). The calculated risk ratio is 0.90 (95% CI, 0.67-1.20) for MF/F vs MF and 0.56 (95% CI 0.44, 0.72) for MF/F vs F.

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.

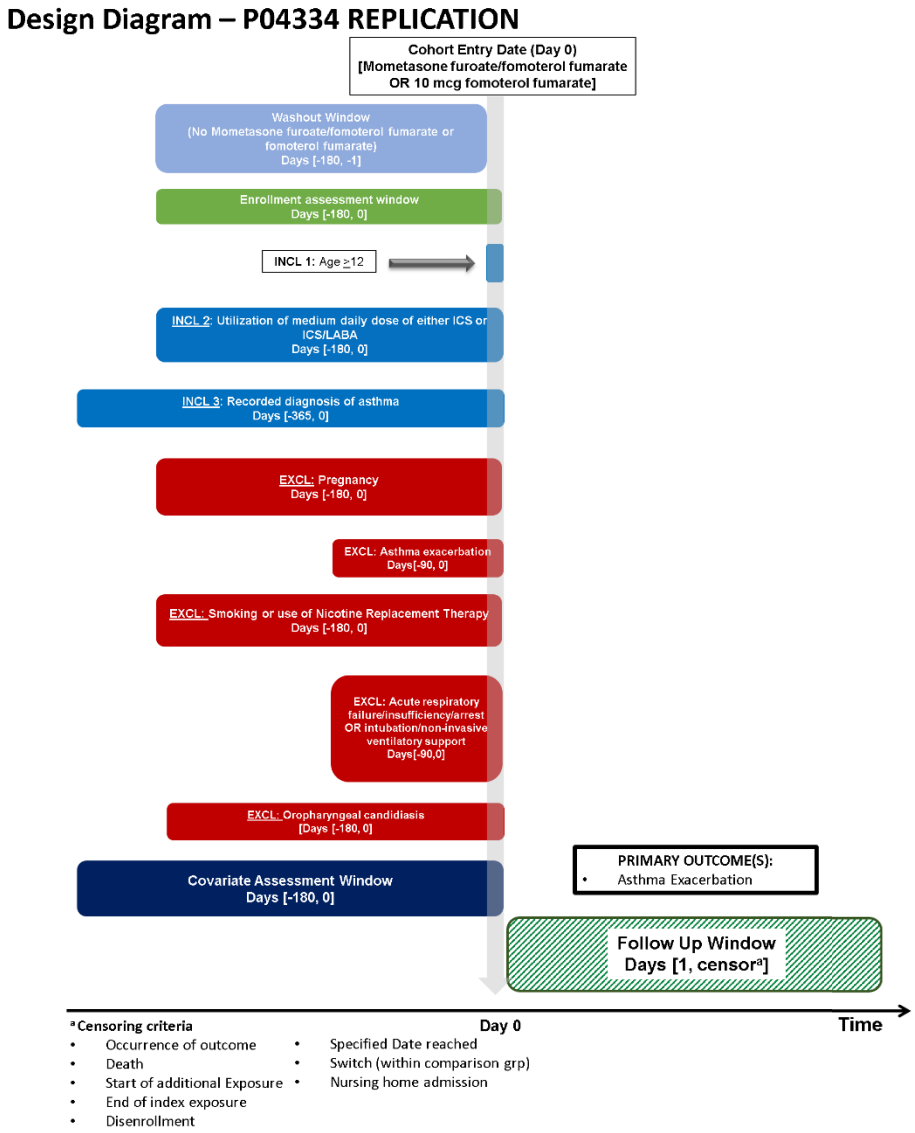
3. Data Source(s)

Optum CDM, IBM® MarketScan®

4. Study Design Diagram

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

Figure 1. Design Diagram – P04334AM1 TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort design comparing mometasone-furoate/formoterol 200/10ug with formoterol 12 ug in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. The patients will be required to have continuous enrollment during a baseline period of 180 days before initiation of mometasone-furoate/formoterol or formoterol. (Note: the formoterol dose used in the trial was 10ug ; in the replication, we will use the market available dose which is 12 ug).

5.2 Important steps for cohort formation

New use of mometasone-furoate/formoterol 200/10ug (exposure) is defined as no use of the exposure drug within the 180 days prior to index date. New use of formoterol 12 ug (comparator) is defined as no use of the comparator drug within the 180 days prior to index date. New users of mometasone-furoate/formoterol 200/10ug are not allowed to receive formoterol 12 ug within the 180 days prior to index date, and new users of formoterol 12 ug are not allowed to receive mometasone-furoate/formoterol 200/10ug within the 180 prior to index date.

5.2.1 Eligible cohort entry dates

Mometasone-furoate/formoterol was approved by FDA on June 24, 2010 for the management of asthma. The initial eligible cohort entry date was the first date after June 24, 2010 for both the databases investigated (IBM® MarketScan®, Optum CDM). The last date eligible as cohort entry date was the end of available data for IBM® MarketScan® and Optum CDM. The following eligible cohort entry dates were included:

- Optum CDM: June 24, 2010 – June 30, 2020 (end of available data)
- IBM® MarketScan®: June 24, 2010– December 31, 2018 (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 Mometasone-furoate/formoterol vs. formoterol

	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	-78,142,188	60,448	-200,050,120	153,788
Excluded due to insufficient enrollment	-8,307	52,141	-16,744	137,044
Excluded due to prior use of referent	-6,358	45,783	-12,623	124,421
Excluded due to prior use of exposure	-20,136	25,647	-47,830	76,591
Excluded because patient qualified in >1 exposure category	0	25,647	-4	76,587
Excluded based on Age : Exclude missing	0	25,647	0	76,587
Excluded based on Gender: Exclude missing	0	25,647	0	76,587
Excluded based on INCLUSION: Age >=12	-1,268	24,379	-3,895	72,692
Excluded based on Inclusion 3 - Medium dose ICS [-90,0]	-21,414	2,965	-60,543	12,149
Excluded based on Inclusion 4 - Asthma [-365, 0]	-587	2,378	-1,947	10,202
Excluded based on Inclusion 8 - Pregnancy	-7	2,371	-14	10,188
Excluded based on Exclusion 4/5 - Asthma exacerbation, respiratory failutre, Intubation [-90,0]	-890	1,481	-1,153	9,035
Excluded based on Exclusion 6 - Smoking	-63	1,418	-112	8,923
Excluded based on Exclusion 8 - Oropharyngeal candidiasis	-4	1,414	-40	8,883
Final cohort		1,414		8,883

6. Variables

6.1 Exposure-related variables:

Study drug:
New initiation of MF/F (200/10 ug twice daily). New initiation is defined as no use of MF/F in the prior 180 days before treatment initiation (washout period). New users of MF/F are not allowed to receive F within the 180 days prior to treatment initiation.

Comparator agent:
New initiation of F (12 ug weekly). F 12ug is the market available dose form of formoterol that was selected for formoterol 10 ug used in the trial. New initiation is defined as no use of F in the prior 180 days before treatment initiation (washout period). New users of F are not allowed to receive MF/F 200/10 ug within the 180 days prior to 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:** Time to first asthma exacerbation (algorithm adapted from Nathan, et. al, and Fuhlbrigge A, et. al.,)

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.

For the AT analyses, the follow-up will start the day after initiation of MF/F and F 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,
- Discontinuation of the index drugs,
- 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 (MF/F and comparator) plus a defined grace period (i.e., 60 days after the end of the last prescription's days' supply in main analyses).
- The date of augmentation or switching from exposure to comparator or vice versa
    - A dosage change on the index treatment does not fulfill this criterion

7. Initial Feasibility Analysis

Aetion report name:

For Mometasone-furoate/formoterol vs. formoterol
Optum CDM - https://bwh-dope.aetion.com/projects/details/1659/results/67130/result/0
IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1658/results/66759/result/0

Date conducted: 03/07/2021 (Marketscan), 3/17/2021 (Optum)

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 Mometasone-furoate/formoterol vs. formoterol

Optum CDM - https://bwh-dope.aetion.com/projects/details/1659/results/67142/result/0
IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1658/results/66760/result/0

Date conducted: 03/07/2021 (Marketscan), 3/17/2021 (Optum)

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:	4/2/2021
Reasons for stopping analysis (if required):			

9. Balance Assessment

For Mometasone-furoate/formoterol vs. formoterol

Optum CDM: https://bwh-dope.aetion.com/projects/details/1659/rwrs/68458
IBM® MarketScan®: https://bwh-dope.aetion.com/projects/details/1658/rwrs/68457

Date conducted:
04/14/2021

After review of initial 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 (0.00%)	0 (0.00%)	0 (0.00%)
Death	2 (0.09%)	2 (0.09%)	0 (0.00%)
Start of an additional exposure	10 (0.46%)	6 (0.28%)	4 (0.18%)
End of index exposure	1747 (80.58%)	882 (40.68%)	865 (39.90%)
Specified date reached	4 (0.18%)	0 (0.00%)	4 (0.18%)
End of patient data	0 (0.00%)	0 (0.00%)	0 (0.00%)
End of patient enrollment	391 (18.04%)	185 (8.53%)	206 (9.50%)
Nursing home admission, pharmacy disenrollment	14 (0.65%)	9 (0.42%)	5 (0.23%)

- Report follow-up time by treatment group.

Median Follow-Up Time (Days) [IQR]		
Patient Group	**Optum**	**Marketscan**
Overall Patient Population	133.5 [88,193]	141.5 [88,214]
Referent	123 [88,157]	147 [88, 207]
Exposure	138 [88,254]	132 [88,222]

- Report overall risk of the primary outcome.

	Optum CDM	IBM® MarketScan®	Pooled
Risk per 1,000 patients	125.88	144.24	141.6

10. Final Power Assessment

Date conducted: 4/15/2021

- 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	2,168
Reference	1,084
Exposed	1,084
Risk per 1,000 patients	141.60
Desired HR from RCT	0.28
Alpha (2-sided)	0.05
Number of events expected	306.9888
Power	1

    - Optum CDM

Superiority Analysis	
Number of patients matched	330
Reference	165
Exposed	165
Risk per 1,000 patients	125.88
Desired HR from RCT	0.28
Alpha (2-sided)	0.05
Number of events expected	41.5404
Power	0.98391473

- IBM® MarketScan®

Superiority Analysis	
Number of patients matched	1,838
Reference	919
Exposed	919
Risk per 1,000 patients	144.24
Desired HR from RCT	0.28
Alpha (2-sided)	0.05
Number of events expected	265.11312
Power	1

- 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:	4/16/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	4/30/2021
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:

13.1 For primary analysis:

13.2 For sensitivity analyses:

14. Requested Results

14.1 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						
…						

14.2 Table 2: Follow-up time

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

14.3 Table 3: Censoring events

	Overall	Referent	Exposure
Dummy outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
Nursing home admission, pharmacy disenrollment			

14.4 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.

14.5 Table 5: Results from secondary analyses.

15. References

Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S34-S48. doi:10.1016/j.jaci.2011.12.983

Nathan RA, Nolte H, Pearlman DS; P04334 Study Investigators. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy Asthma Proc. 2010 Jul-Aug;31(4):269-79. doi: 10.2500/aap.2010.31.3364. Epub 2010 Jul 30. PMID: 20678306.

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

Appendix A

#	P04334AM1 trial definitions	Implementation in routine care	Please see the following Google Drive for further details or any missing information: https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV?usp=sharing 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	Reference/Rationale
	Trial details- clinicaltrials.gov NCT00383240			
	EXPOSURE vs. COMPARISON			
	Exposure) Mometasone furoate/formoterol fumarate combination MDI 200/10 mcg BID vs. Referent) Formoterol fumarate 10 mcg	**Exposure:**Mometasone furoate/formoterol fumarate 200/10 mcg BID NDC code: 00085720601 00085720607 **Referent:** formoterol fumarate 10 mcg NDC code: 54569525400 - formoterol fumarate 54868497200 - formoterol fumarate 54868497201 - formoterol fumarate 00083016702 - formoterol fumarate 00083016711 - formoterol fumarate 00083016774 - formoterol fumarate 00085140101 - formoterol fumarate 00085140201 - formoterol fumarate 00085140202 - formoterol fumarate 68115065160 - formoterol fumarate		
	PRIMARY OUTCOME			
	Time-to-first Asthma Exacerbation	**Measured 1 day after drug initiation** 1) Asthma diagnosis code in inpatient primary diagnosis position 2) Asthma diagnosis code in inpatient any position or outpatient setting PLUS a prescription claim for systemic steroids 14 days before and after the diagnosis code Asthma: ICD-9: 493.x ICD-10 : J45.*		
	INCLUSION CRITERIA			
1	Informed Consent: A signed and dated written informed consent prior to study participation	N/A		
2	Age ≥ 12 years, adult and adolescent subjects	**Measured on the day of drug of initiation** Age >=12		
3	A subject must have been using a medium daily dose of inhaled glucocorticosteroid (ICS) (either alone or in combination with a long-acting beta agonist (LABA)) for at least 12 weeks and must have been on a stable regimen (daily dose unchanged) for at least 2 weeks prior to Screening. Medium daily doses of ICS are defined as follows: >500 to 1000 mcg beclomethasone chlorofluorocarbon (CFC) >250 to 500 mcg beclomethasone hydrofluoroalkane (HFA) >600 to 1000 mcg budesonide dry powder inhaler (DPI) >1000 to 2000 mcg flunisolide >250 to 500 mcg fluticasone 400 mcg MF >1000 to 2000 mcg triamcinolone acetonide	**Measured 90 days prior to drug initiation** See tab [medium dose ICS] for NDC codes		
4	To document the diagnosis of asthma and assure the subject's responsiveness to bronchodilators before randomization one of the following methods can be used at the Screening Visit, Day -14, or thereafter, but prior to the Baseline Visit:	**Measured 365 days prior to cohort entry in any position, any setting** Asthma: ICD-9: 493.x ICD-10 : J45.*	Larsson K, Ställberg B, Lisspers K, Telg G, Johansson G, Thuresson M, Janson C. Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). Respir Res. 2018 Jan 18;19(1):12. doi: 10.1186/s12931-018-0719-x. PMID: 29347939; PMCID: PMC5774144.	
	The subject must demonstrate an increase in absolute FEV1 of at least 12% and at least 200 mL within 15 minutes after administration of four inhalations of albuterol/salbutamol (total dose of 360 to 400 mcg) or of nebulized SABA (2.5 mg) if confirmed as standard office practice, OR The subject must demonstrate a peak expiratory flow (PEF) variability of more than 20% expressed as a percentage of the highest and lowest morning prebronchodilator PEF over at least 1 week OR The subject must demonstrate a diurnal variation in PEF of more than 20% based on the difference between the prebronchodilator morning value and the postbronchodilator value from the evening before, expressed as a percentage of the mean daily PEF value.	N/A		
5	At the Screening Visit, the subject's FEV1 must be ≥60% and ≤90% predicted.	N/A		
6	At the Baseline Visit, the subject's FEV1 must be ≥60% and ≤85% predicted when all restricted medications have been withheld for the appropriate intervals.	N/A		
7	Clinical laboratory tests (complete blood counts [CBC], blood chemistries, and urinalysis) conducted at the Screening Visit must be within normal limits or clinically acceptable to the investigator/sponsor. An electrocardiogram (ECG) using a centralized trans-telephonic technology at the Screening Visit must be clinically acceptable to the investigator. A chest x-ray performed at the Screening Visit, or within 12 months prior to the Screening Visit, must be clinically acceptable to the investigator.	N/A		

Color Coding Criteria

- Can be replicated in claims
- Using dummy definitions for measuring in claims
- Can't be measured in claims
- Can't be measured in claims but not important for the analysis

Appendix A

8	A female subject of childbearing potential must have been using a medically acceptable, adequate form of birth control. This includes: 1) hormonal contraceptives as prescribed by a physician (oral combined, hormonal implant); 2) medically prescribed intra-uterine device (IUD); 3) condom in combination with a spermicide (double barrier method); 4) monogamous relationship with a male partner who has had a vasectomy. The subject must have started this birth control method at least 3 months prior to Screening (with the exception of condom in combination with spermicide), and must agree to continue its use for the duration of the study. A female subject of childbearing potential who is not currently sexually active must agree and consent to using a medically acceptable birth control method should she become sexually active during the course of this study. Women who have been surgically sterilized or are at least 1 year postmenopausal are not considered to be of childbearing potential. A female subject of childbearing potential must have a negative serum pregnancy test at Screening in order to be considered eligible for enrollment.	**Measured 180 days prior to drug initiation in any setting and position** See tab [pregnancy] ; will be applied as an exclusion.	
	EXCLUSION CRITERIA		
1	A subject who demonstrates a change (increase or decrease) in absolute FEV1 of >20% at any time from the Screening Visit up to and including the Baseline Visit.	N/A	
2	A subject who requires the use of greater than eight inhalations per day of SABA MDI, or two or more nebulized treatments per day of 2.5 mg SABA, on any 2 consecutive days from the Screening Visit up to and including the Baseline Visit.	N/A	
3	A subject who experiences a decrease in AM or PM PEF below the Screening Period stability limit on any 2 consecutive days prior to Randomization.	N/A	
4	A subject who experiences an occurrence of any clinical deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with additional, excluded asthma medication (other than SABA) as judged by the clinical investigator at any time from the Screening Visit up to and including the Baseline Visit.	**Measured 90 days prior to drug initiation** Asthma exacerbation 1) Asthma diagnosis code in inpatient primary diagnosis position 2) Asthma diagnosis code in inpatient any position or outpatient setting PLUS a prescription claim for systemic steroids 14 days before and after the diagnosis code	
5	Emergency room treatment for asthma deterioration requiring systemic corticosteroid therapy or hospitalization for managemenet of airway obstruction within the 3 months before baseline	Asthma: ICD-9: 493.x ICD-10 : J45.* or Acute respiratory failure/insufficiency/arrest ICD-9: "517.3", "518.5", "518.81", "518.82", "518.83", "518.84", "799.1", "V46.1", "V46.11", "V46.12", "V46.13", "V46.14", "V46.2" ICD-10: "J80", "J96.00", "J96.01", "J96.02", "J96.10", "J96.11", "J96.12", "J96.20", "J96.21", "J96.22", "J96.90", "J96.91", "J96.92", "R09.01", "R09.2", "Z99.11", "Z99.12", "Z99.81" } Intubation/Non-invasive ventilatory support: ICD-9 Procedure code: "93.90", "93.92", "96.01", "96.02", "96.03", "96.04", "96.05", "96.70", "96.71", "96.72" ICD-10 procedure codes: "09HN7BZ", "09HN8BZ", "0BH13EZ", "0BH17EZ", "0BH18EZ", "0CHY7BZ", "0CHY8BZ", "0DH57BZ", "0DH58BZ", "0WHQ73Z", "0WHQ7YZ", "5A09357", "5A09457", "5A09557", "5A1935Z", "5A1945Z", "5A1955Z" }	Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: a population-based study. Ann Am Thorac Soc. 2013 Feb;10(1):10-7. doi: 10.1513/AnnalsATS.201206-034OC. PMID: 23509327; PMCID: PMC3780971.
6	A subject who is a smoker or ex-smoker and has smoked within the previous year or has had a cumulative smoking history >10 pack-years	**Measured 180 days prior to drug initiation in any setting, any position** ICD-9/10 codes: V15.82, 305.1x, 649.0x, 989.84 OR CPT code 99406, 99407, G0436, G0437, G9016, S9075, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F OR use of varenicline tartrate or nicotine replacement therapy ("Nicotine", "Nicotine Bitartrate", and "Nicotine Polacrilex")	
6	Patients requiring concomitant asthma medication	N/A	
7	Clinically significant abnormal vital sign	N/A	
8	Visible evidence of oropharyngeal candidiasis at baseline or earlier	**Measured 180 days prior to drug initiation in any setting, any position** Oropharyngeal candidiasis: ICD-9: 112.0 ICD-10: B37.0, B37.83	

Appendix A

NDC codes for medium dose ICS
37024523
85134107
85433401
85461001
173049500
173050400
173060100
173060102
173069604
173071700
173071722
173072000
173072020
173075300
173085914
173087414
173088710
173088714
21695019601
23490754201
35356009914
49999061412
49999081960
54569524200
54569566300
54868554700
54868563700
55045335400
58016481201
59310071106
68115092460
68258303101
85134101
85134102

Appendix A

85134103
85134104
85134106
85461005
93360982
173049900
173060202
173069600
173069602
173071720
173085910
173088810
49999061401
54569460200
54569460300
54569570200
54868439200
54868451700
54868554701
54868554702
55045291901
55045368601
58016460401
59310072206
59310082206
68115063713
68258891306

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
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

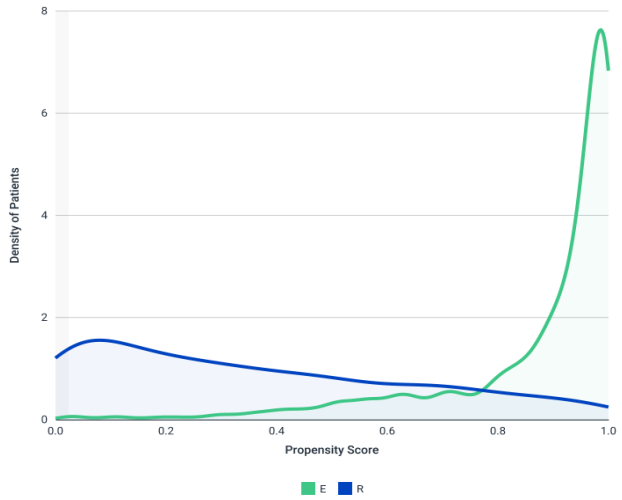
Appendix A

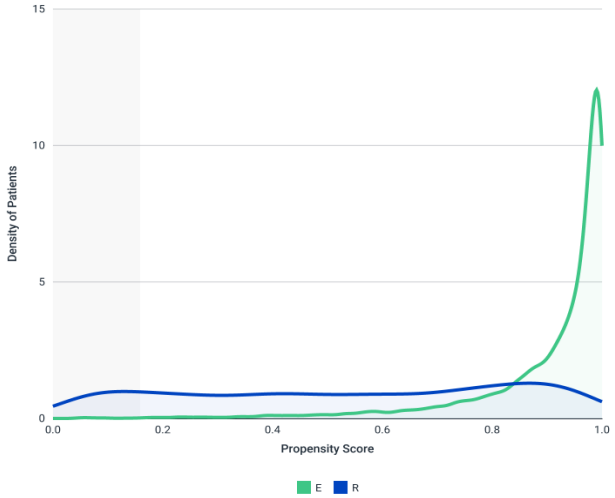
72.53 TOTAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.54 OTHER TOTAL BREECH EXTRACTION
72.6 FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7 VACUUM EXTRACTION
72.71 VACUUM EXTRACTION WITH EPISIOTOMY
72.79 OTHER VACUUM EXTRACTION
72.8 OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9 UNSPECIFIED INSTRUMENTAL 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
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
74.2 EXTRAPERITONEAL CESAREAN SECTION
74.3 REMOVAL OF EXTRATUBAL ECTOPIC PREGNANCY
74.4 CESAREAN SECTION OF OTHER SPECIFIED TYPE
74.9 CESAREAN SECTION OF UNSPECIFIED TYPE
74.91 HYSTEROTOMY TO TERMINATE PREGNANCY
74.99 OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
75.4 MANUAL REMOVAL OF RETAINED PLACENTA
75.5 REPAIR OF CURRENT OBSTETRIC LACERATION OF UTERUS
75.6 REPAIR OF OTHER CURRENT OBSTETRIC LACERATION
75.7 MANUAL EXPLORATION OF UTERINE CAVITY, POSTPARTUM
75.9 OTHER OBSTETRIC OPERATIONS

Appendix B

Optum	MarketScan

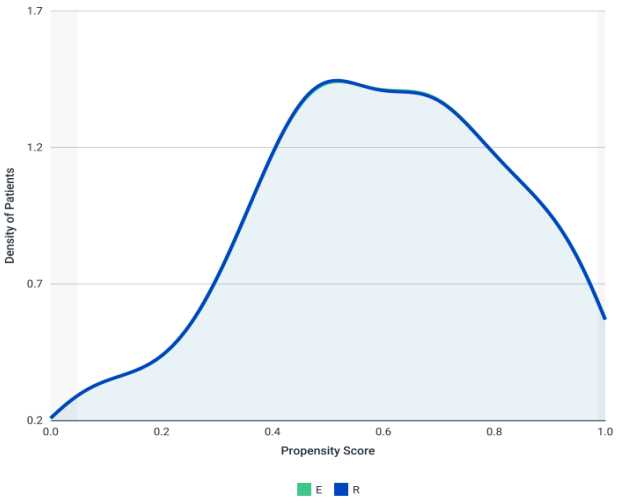
BEFORE PS MATCHING

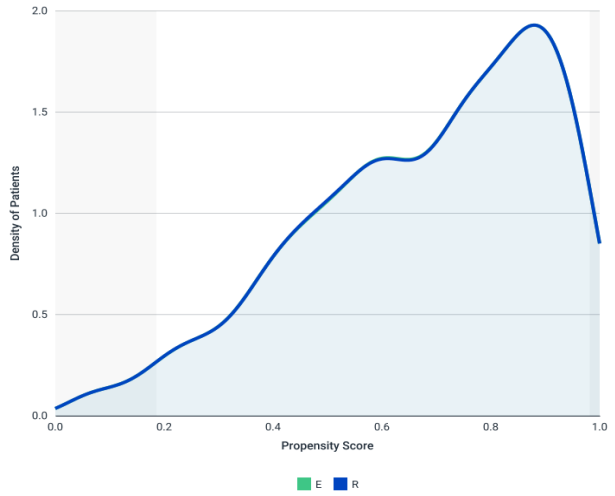




The c-statistics for the propensity score model, pre-matching was 0.924. The postmatching c-statistic was 0.683.	The c-statistics for the propensity score model, pre-matching was 0.891. The postmatching c-statistic was 0.573.

AFTER PS MATCHING





Appendix B

	Unmatched								
	Optum			Marketscan			POOLED		
Variable	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.
Number of patients	**363**	**1,051**		**1,325**	**7,549**		**1,688**	**8,600**	
Year of Cohort Entry Date									
...2010; n (%)	78 (21.5%)	7 (0.7%)	0.062	305 (23.0%)	112 (1.5%)	0.061	383 (22.7%)	119 (1.4%)	0.692
...2011; n (%)	115 (31.7%)	121 (11.5%)	0.044	385 (29.1%)	992 (13.1%)	0.035	500 (29.6%)	1,113 (12.9%)	0.417
...2012; n (%)	67 (18.5%)	173 (16.5%)	0.005	258 (19.5%)	1,275 (16.9%)	0.006	325 (19.3%)	1,448 (16.8%)	0.065
...2013; n (%)	41 (11.3%)	174 (16.6%)	-0.014	143 (10.8%)	1,173 (15.5%)	-0.013	184 (10.9%)	1,347 (15.7%)	-0.142
...2014; n (%)	37 (10.2%)	163 (15.5%)	-0.015	142 (10.7%)	1,700 (22.5%)	-0.029	179 (10.6%)	1,863 (21.7%)	-0.305
...2015; n (%)	20 (5.5%)	142 (13.5%)	-0.026	79 (6.0%)	846 (11.2%)	-0.018	099 (5.9%)	988 (11.5%)	-0.200
...2016; n (%)	5 (1.4%)	124 (11.8%)	-0.041	13 (1.0%)	679 (9.0%)	-0.036	018 (1.1%)	803 (9.3%)	-0.376
...2017; n (%)	0 (0.0%)	59 (5.6%)	-0.033	0 (0.0%)	500 (6.6%)	-0.036	000 (0.0%)	559 (6.5%)	-0.373
...2018; n (%)	0 (0.0%)	30 (2.9%)	-0.024	0 (0.0%)	272 (3.6%)	-0.027	000 (0.0%)	302 (3.5%)	-0.269
...2019; n (%)	0 (0.0%)	34 (3.2%)	-0.025	NA	NA	NA	NA	NA	NA
...2020; n (%)	0 (0.0%)	24 (2.3%)	-0.021	NA	NA	NA	NA	NA	NA
Age									
...mean (sd)	55.26 (15.34)	50.76 (17.81)	0.271	56.57 (15.86)	46.67 (18.21)	0.580	56.29 (15.75)	47.17 (18.16)	0.537
...median [IQR]	57.00 [48.00, 65.00]	53.00 [40.00, 63.00]	0.241	59.00 [48.00, 65.00]	50.00 [34.00, 60.00]	0.527	58.57 (15.75)	50.37 (18.16)	0.482
Age categories									
...12-17; n (%)	11 (3.0%)	68 (6.5%)	-0.016	35 (2.6%)	800 (10.6%)	-0.031	046 (2.7%)	868 (10.1%)	-0.306
...18-39; n (%)	39 (10.7%)	182 (17.3%)	-0.018	124 (9.4%)	1,588 (21.0%)	-0.030	163 (9.7%)	1,770 (20.6%)	-0.308
...40 - 64; n (%)	221 (60.9%)	574 (54.6%)	0.008	814 (61.4%)	4,178 (55.3%)	0.008	1,035 (61.3%)	4,752 (55.3%)	0.122
...>= 65; n (%)	92 (25.3%)	227 (21.6%)	0.008	352 (26.6%)	983 (13.0%)	0.031	444 (26.3%)	1,210 (14.1%)	0.307
Geographic Region									
...Northeast; n (%)	46 (12.7%)	97 (9.2%)	0.011	332 (25.1%)	1,239 (16.4%)	0.019	378 (22.4%)	1,336 (15.5%)	0.177
...South; n (%)	163 (44.9%)	392 (37.3%)	0.012	447 (33.7%)	2,643 (35.0%)	-0.002	610 (36.1%)	3,035 (35.3%)	0.017
...Midwest; n (%)	86 (23.7%)	372 (35.4%)	-0.022	307 (23.2%)	1,605 (21.3%)	0.004	393 (23.3%)	1,977 (23.0%)	0.007
...West; n (%)	68 (18.7%)	190 (18.1%)	0.001	222 (16.8%)	1,972 (26.1%)	-0.020	290 (17.2%)	2,162 (25.1%)	-0.194
...Unknown/Missing; n (%)	NA	NA	NA	17 (1.3%)	90 (1.2%)	0.001	NA	NA	NA
Metropolitan Statistical Area									
...Urban; n (%)	NA	NA	NA	1,090 (82.3%)	6,106 (80.9%)	0.002	NA	NA	NA
...Rural; n (%)	NA	NA	NA	2 (0.2%)	132 (1.7%)	-0.015	NA	NA	NA
...Unknown/Missing; n (%)	NA	NA	NA	233 (17.6%)	1,311 (17.4%)	0.000	NA	NA	NA
General Health Related Measures									
Alcohol/Drug abuse or dependence ; n (%)	6 (1.7%)	23 (2.2%)	-0.004	18 (1.4%)	76 (1.0%)	0.004	024 (1.4%)	099 (1.2%)	0.018
Obesity or Overweight; n (%)	39 (10.7%)	133 (12.7%)	-0.006	104 (7.8%)	694 (9.2%)	-0.005	143 (8.5%)	827 (9.6%)	-0.038
Obesity; n (%)	35 (9.6%)	109 (10.4%)	-0.003	93 (7.0%)	594 (7.9%)	-0.003	128 (7.6%)	703 (8.2%)	-0.022
Overweight; n (%)	4 (1.1%)	27 (2.6%)	-0.011	14 (1.1%)	112 (1.5%)	-0.004	018 (1.1%)	139 (1.6%)	-0.043
Cardiovascular Measures									
Hypertension; n (%)	165 (45.5%)	403 (38.3%)	0.011	537 (40.5%)	2,096 (27.8%)	0.022	702 (41.6%)	2,499 (29.1%)	0.264
Hyperlipidemia; n (%)	135 (37.2%)	320 (30.4%)	0.012	419 (31.6%)	1,621 (21.5%)	0.020	554 (32.8%)	1,941 (22.6%)	0.229
MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	39 (10.7%)	56 (5.3%)	0.019	159 (12.0%)	300 (4.0%)	0.028	198 (11.7%)	356 (4.1%)	0.285
Old MI; n (%)	6 (1.7%)	7 (0.7%)	0.009	12 (0.9%)	20 (0.3%)	0.008	018 (1.1%)	027 (0.3%)	0.096
Acute MI; n (%)	2 (0.6%)	3 (0.3%)	0.004	8 (0.6%)	10 (0.1%)	0.008	010 (0.6%)	013 (0.2%)	0.063
Stable angina; n (%)	5 (1.4%)	5 (0.5%)	0.009	16 (1.2%)	47 (0.6%)	0.006	021 (1.2%)	052 (0.6%)	0.064
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	36 (9.9%)	52 (4.9%)	0.018	143 (10.8%)	252 (3.3%)	0.028	179 (10.6%)	304 (3.5%)	0.280
History of CABG or PTCA; n (%)	4 (1.1%)	11 (1.0%)	0.001	14 (1.1%)	28 (0.4%)	0.008	018 (1.1%)	039 (0.5%)	0.067
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)	7 (1.9%)	16 (1.5%)	0.003	21 (1.6%)	62 (0.8%)	0.007	028 (1.7%)	078 (0.9%)	0.071
Stroke (Ischemic or hemorrhagic); n (%)	7 (1.9%)	8 (0.8%)	0.009	13 (1.0%)	31 (0.4%)	0.007	020 (1.2%)	039 (0.5%)	0.076
TIA; n (%)	0 (0.0%)	8 (0.8%)	-0.013	10 (0.8%)	24 (0.3%)	0.007	010 (0.6%)	032 (0.4%)	0.028
Late effects of cerebrovascular disease; n (%)	2 (0.6%)	4 (0.4%)	0.003	7 (0.5%)	19 (0.3%)	0.003	009 (0.5%)	023 (0.3%)	0.032
Atrial fibrillation and Other cardiac dysrhythmia; n (%)	25 (6.9%)	75 (7.1%)	-0.001	108 (8.2%)	320 (4.2%)	0.016	133 (7.9%)	395 (4.6%)	0.137
Atrial fibrillation; n (%)	10 (2.8%)	40 (3.8%)	-0.006	64 (4.8%)	150 (2.0%)	0.015	074 (4.4%)	190 (2.2%)	0.123
Other cardiac dysrhythmia; n (%)	20 (5.5%)	59 (5.6%)	0.000	65 (4.9%)	231 (3.1%)	0.009	085 (5.0%)	290 (3.4%)	0.080
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)	52 (14.3%)	155 (14.7%)	-0.001	227 (17.1%)	706 (9.4%)	0.021	279 (16.5%)	861 (10.0%)	0.193

Appendix B

Diabetes mellitus without mention of complications; n (%)	50 (13.8%)	149 (14.2%)	-0.001	214 (16.2%)	670 (8.9%)	0.021	264 (15.6%)	819 (9.5%)	0.185
Diabetes with specified complications; n (%)	9 (2.5%)	40 (3.8%)	-0.007	52 (3.9%)	119 (1.6%)	0.014	061 (3.6%)	159 (1.8%)	0.111
Diabetes with unspecified complications; n (%)	2 (0.6%)	4 (0.4%)	0.003	10 (0.8%)	24 (0.3%)	0.007	012 (0.7%)	028 (0.3%)	0.057
GI Conditions									
GERD; n (%)	57 (15.7%)	195 (18.6%)	-0.007	171 (12.9%)	1,014 (13.4%)	-0.001	228 (13.5%)	1,209 (14.1%)	-0.017
Upper GI (Diseases of esophagus, stomach and duodenum including GERD) ; n (%)	68 (18.7%)	217 (20.6%)	-0.004	222 (16.8%)	1,216 (16.1%)	0.002	290 (17.2%)	1,433 (16.7%)	0.013
GI bleeding; n (%)	9 (2.5%)	14 (1.3%)	0.009	21 (1.6%)	85 (1.1%)	0.004	030 (1.8%)	099 (1.2%)	0.049
Non-infective enteritis and colitis; n (%)	13 (3.6%)	49 (4.7%)	-0.005	62 (4.7%)	257 (3.4%)	0.006	075 (4.4%)	306 (3.6%)	0.041
Intraoperative and postprocedural complications and disorders of digestive system; n (%)	10 (2.8%)	16 (1.5%)	0.009	26 (2.0%)	106 (1.4%)	0.005	036 (2.1%)	122 (1.4%)	0.053
Disorders of gallbladder, biliary tract and pancreas; n (%)	1 (0.3%)	18 (1.7%)	-0.014	15 (1.1%)	82 (1.1%)	0.000	016 (0.9%)	100 (1.2%)	-0.029
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)	5 (1.4%)	29 (2.8%)	-0.010	23 (1.7%)	86 (1.1%)	0.005	028 (1.7%)	115 (1.3%)	0.033
Osteoarthrosis; n (%)	51 (14.0%)	122 (11.6%)	0.007	148 (11.2%)	571 (7.6%)	0.012	199 (11.8%)	693 (8.1%)	0.124
Other rheumatic disorders (including gout); n (%)	103 (28.4%)	278 (26.5%)	0.004	368 (27.8%)	1,529 (20.3%)	0.015	471 (27.9%)	1,807 (21.0%)	0.161
Gout and other crystal arthropathies; n (%)	9 (2.5%)	21 (2.0%)	0.003	20 (1.5%)	76 (1.0%)	0.004	029 (1.7%)	097 (1.1%)	0.051
Other rheumatic disorders; n (%)	95 (26.2%)	263 (25.0%)	0.002	353 (26.6%)	1,473 (19.5%)	0.015	448 (26.5%)	1,736 (20.2%)	0.149
Neuro Conditions									
Alzheimer and other Dementia Disease ; n (%)	5 (1.4%)	12 (1.1%)	0.003	15 (1.1%)	46 (0.6%)	0.005	020 (1.2%)	058 (0.7%)	0.052
Seizure disorders (epilepsy); n (%)	1 (0.3%)	8 (0.8%)	-0.007	10 (0.8%)	29 (0.4%)	0.005	011 (0.7%)	037 (0.4%)	0.041
Delirium/Psychosis; n (%)	4 (1.1%)	14 (1.3%)	-0.002	16 (1.2%)	50 (0.7%)	0.005	020 (1.2%)	064 (0.7%)	0.052
Other Conditions									
Hypothyroidism; n (%)	31 (8.5%)	128 (12.2%)	-0.012	135 (10.2%)	722 (9.6%)	0.002	166 (9.8%)	850 (9.9%)	-0.003
Chronic kidney disease stages I-III; n (%)	14 (3.9%)	39 (3.7%)	0.001	32 (2.4%)	118 (1.6%)	0.006	046 (2.7%)	157 (1.8%)	0.061
Chronic kidney disease stages IV-V, ESRD; n (%)	4 (1.1%)	11 (1.0%)	0.001	17 (1.3%)	51 (0.7%)	0.006	021 (1.2%)	062 (0.7%)	0.052
COPD; n (%)	83 (22.9%)	152 (14.5%)	0.019	294 (22.2%)	607 (8.0%)	0.037	377 (22.3%)	759 (8.8%)	0.379
Obstructive sleep apnea; n (%)	46 (12.7%)	111 (10.6%)	0.006	166 (12.5%)	600 (7.9%)	0.014	212 (12.6%)	711 (8.3%)	0.141
Syncope; n (%)	4 (1.1%)	23 (2.2%)	-0.009	23 (1.7%)	91 (1.2%)	0.004	027 (1.6%)	114 (1.3%)	0.025
Falls; n (%)	6 (1.7%)	21 (2.0%)	-0.002	6 (0.5%)	53 (0.7%)	-0.003	012 (0.7%)	074 (0.9%)	-0.022
VTE; n (%)	6 (1.7%)	14 (1.3%)	0.003	20 (1.5%)	67 (0.9%)	0.005	026 (1.5%)	081 (0.9%)	0.055
Combined comorbidity score, 365 days									
...mean (sd)	1.48 (1.68)	1.55 (1.65)	-0.042	1.49 (1.58)	1.24 (1.16)	0.180	1.49 (1.60)	1.28 (1.23)	0.147
...median [IQR]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.000	1.00 [1.00, 2.00]	1.00 [1.00, 1.00]	0.000	1.00 (1.60)	1.00 (1.23)	0.000
Frailty Score: Empirical Version 365 days as Categories									
...< 0.1 non frail; n (%)	163 (44.9%)	622 (59.2%)	-0.020	512 (38.6%)	4,595 (60.9%)	-0.032	675 (40.0%)	5,217 (60.7%)	-0.423
...0.1 - < 0.2 prefrail; n (%)	98 (27.0%)	247 (23.5%)	0.007	371 (28.0%)	1,742 (23.1%)	0.010	469 (27.8%)	1,989 (23.1%)	0.108
... > 0.2 frail; n (%)	102 (28.1%)	182 (17.3%)	0.023	442 (33.4%)	1,212 (16.1%)	0.035	544 (32.2%)	1,394 (16.2%)	0.380
Medication Use									
Use of oral corticosteroids; n (%)	181 (49.9%)	507 (48.2%)	0.002	663 (50.0%)	3,950 (52.3%)	-0.003	844 (50.0%)	4,457 (51.8%)	-0.036
Use of antidepressants; n (%)	95 (26.2%)	279 (26.5%)	-0.001	304 (22.9%)	1,802 (23.9%)	-0.002	399 (23.6%)	2,081 (24.2%)	-0.014
Use of anticonvulsants; n (%)	27 (7.4%)	123 (11.7%)	-0.014	157 (11.8%)	649 (8.6%)	0.010	184 (10.9%)	772 (9.0%)	0.064
Use of beta blocker OR calcium channel blocker; n (%)	72 (19.8%)	185 (17.6%)	0.005	285 (21.5%)	964 (12.8%)	0.021	357 (21.1%)	1,149 (13.4%)	0.205
Use of PPIs; n (%)	84 (23.1%)	221 (21.0%)	0.004	384 (29.0%)	1,884 (25.0%)	0.008	468 (27.7%)	2,105 (24.5%)	0.073
Use of opioids; n (%)	88 (24.2%)	249 (23.7%)	0.001	369 (27.8%)	1,516 (20.1%)	0.016	457 (27.1%)	1,765 (20.5%)	0.155
Use of antipsychotics; n (%)	4 (1.1%)	27 (2.6%)	-0.011	28 (2.1%)	141 (1.9%)	0.001	032 (1.9%)	168 (2.0%)	-0.007
Use of anxiolytics/hypnotics; n (%)	36 (9.9%)	93 (8.8%)	0.004	136 (10.3%)	576 (7.6%)	0.009	172 (10.2%)	669 (7.8%)	0.084
Use of dementia meds; n (%)	2 (0.6%)	2 (0.2%)	0.006	13 (1.0%)	28 (0.4%)	0.007	015 (0.9%)	030 (0.3%)	0.078
Use of antiparkinsonian meds; n (%)	4 (1.1%)	26 (2.5%)	-0.010	37 (2.8%)	107 (1.4%)	0.010	041 (2.4%)	133 (1.5%)	0.065
Use of Benzodiazepine; n (%)	36 (9.9%)	147 (14.0%)	-0.012	193 (14.6%)	909 (12.0%)	0.007	229 (13.6%)	1,056 (12.3%)	0.039
All antidiabetic medications; n (%)	39 (10.7%)	117 (11.1%)	-0.001	176 (13.3%)	626 (8.3%)	0.015	215 (12.7%)	743 (8.6%)	0.133
ACEI/ARB; n (%)	112 (30.9%)	299 (28.4%)	0.005	428 (32.3%)	1,681 (22.3%)	0.019	540 (32.0%)	1,980 (23.0%)	0.203
Use of Anticoagulants; n (%)	12 (3.3%)	37 (3.5%)	-0.001	58 (4.4%)	176 (2.3%)	0.011	070 (4.1%)	213 (2.5%)	0.090
Use of Amiodarone; n (%)	1 (0.3%)	3 (0.3%)	0.000	10 (0.8%)	15 (0.2%)	0.008	011 (0.7%)	018 (0.2%)	0.075
Digoxin; n (%)	2 (0.6%)	5 (0.5%)	0.001	20 (1.5%)	34 (0.5%)	0.010	022 (1.3%)	039 (0.5%)	0.085
Use of Diuretics; n (%)	85 (23.4%)	230 (21.9%)	0.003	365 (27.5%)	1,376 (18.2%)	0.019	450 (26.7%)	1,606 (18.7%)	0.192
Use of Aspirin; n (%)	3 (0.8%)	3 (0.3%)	0.007	10 (0.8%)	44 (0.6%)	0.002	013 (0.8%)	047 (0.5%)	0.037
NSAIDs (NOT including aspirin); n (%)	38 (10.5%)	137 (13.0%)	-0.007	177 (13.4%)	999 (13.2%)	0.001	215 (12.7%)	1,136 (13.2%)	-0.015
HRT (Use of estrogens, progestins, androgens); n (%)	31 (8.5%)	140 (13.3%)	-0.015	160 (12.1%)	1,209 (16.0%)	-0.010	191 (11.3%)	1,349 (15.7%)	-0.129
Use of Statins ; n (%)	109 (30.0%)	287 (27.3%)	0.005	428 (32.3%)	1,626 (21.5%)	0.021	537 (31.8%)	1,913 (22.2%)	0.218

Appendix B

Healthcare Utilization Measures									
Use of any drugs claims									
...mean (sd)	28.06 (20.25)	30.77 (23.08)	-0.125	29.03 (20.42)	27.03 (18.93)	0.102	28.82 (20.38)	27.49 (19.48)	0.067
...median [IQR]	23.00 [13.00, 41.00]	24.00 [16.00, 40.00]	-0.046	25.00 [15.00, 39.00]	22.00 [13.00, 36.00]	0.152	24.57 (20.38)	22.24 (19.48)	0.117
Number of office visits									
...mean (sd)	11.96 (10.10)	13.13 (11.32)	-0.109	12.13 (9.25)	11.25 (10.06)	0.091	12.09 (9.44)	11.48 (10.22)	0.062
...median [IQR]	9.00 [5.00, 15.00]	10.00 [6.00, 17.00]	-0.093	10.00 [5.50, 16.00]	9.00 [5.00, 15.00]	0.103	9.78 (9.44)	9.12 (10.22)	0.067
Number of ED visits									
...mean (sd)	0.52 (1.06)	0.57 (1.62)	-0.037	0.58 (1.40)	0.43 (1.03)	0.122	0.57 (1.33)	0.45 (1.12)	0.098
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.000	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.000	0.00 (1.33)	0.00 (1.12)	0.000
Number of hospitalizations									
...mean (sd)	0.12 (0.63)	0.09 (0.41)	0.056	0.54 (2.44)	0.22 (1.55)	0.157	0.45 (2.18)	0.20 (1.46)	0.135
...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 (2.18)	0.00 (1.46)	0.000
Recent hospitalization (-30 days to Index Rx date); n (%)	2 (0.6%)	16 (1.5%)	-0.009	29 (2.2%)	54 (0.7%)	0.012	031 (1.8%)	070 (0.8%)	0.088
Old hospitalizations (-365 to -31 days); n (%)	42 (11.6%)	113 (10.8%)	0.002	180 (13.6%)	523 (6.9%)	0.021	222 (13.2%)	636 (7.4%)	0.192
Number of Pulmonologist/Allergist visits									
...mean (sd)	0.11 (0.59)	0.07 (0.49)	0.074	1.38 (3.13)	2.03 (4.35)	-0.172	1.11 (2.79)	1.79 (4.08)	-0.195
...median [IQR]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 [0.00, 1.00]	0.00 [0.00, 2.00]	0.000	0.00 (2.79)	0.00 (4.08)	0.000
Pulmonologist /allergist on CED; n (%)	4 (1.1%)	5 (0.5%)	0.007	147 (11.1%)	1,099 (14.6%)	-0.010	151 (8.9%)	1,104 (12.8%)	-0.126
Number of hospital days									
...mean (sd)	1.51 (10.26)	0.74 (4.89)	0.096	0.54 (2.44)	0.22 (1.55)	0.157	0.75 (5.22)	0.28 (2.24)	0.117
...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 (5.22)	0.00 (2.24)	0.000
Occurrence of basic or comprehensive metabolic blood chemistry test; n (%)	149 (41.0%)	406 (38.6%)	0.004	434 (32.8%)	2,074 (27.5%)	0.010	583 (34.5%)	2,480 (28.8%)	0.123
Number of HbA1C test ordered									
...mean (sd)	0.51 (1.00)	0.55 (1.12)	-0.038	0.45 (1.00)	0.38 (0.91)	0.073	0.46 (1.00)	0.40 (0.94)	0.062
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.000	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.000	0.00 (1.00)	0.00 (0.94)	0.000
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	18 (5.0%)	34 (3.2%)	0.009	70 (5.3%)	291 (3.9%)	0.007	088 (5.2%)	325 (3.8%)	0.068
Number of Mammograms (Breast cancer screening); n (%)	46 (12.7%)	151 (14.4%)	-0.005	175 (13.2%)	1,091 (14.5%)	-0.003	221 (13.1%)	1,242 (14.4%)	-0.038
Number of Pap smear (Cervical cancer screening); n (%)	29 (8.0%)	110 (10.5%)	-0.008	107 (8.1%)	814 (10.8%)	-0.009	136 (8.1%)	924 (10.7%)	-0.089
Flu vaccine; n (%)	66 (18.2%)	212 (20.2%)	-0.005	193 (14.6%)	1,316 (17.4%)	-0.007	259 (15.3%)	1,528 (17.8%)	-0.067
Pneumococcal vaccine; n (%)	10 (2.8%)	96 (9.1%)	-0.026	42 (3.2%)	622 (8.2%)	-0.021	052 (3.1%)	718 (8.3%)	-0.226
Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	38.10 (33.36)	37.67 (31.88)	0.013	34.89 (33.21)	26.35 (23.40)	0.297	35.58 (33.24)	27.73 (24.59)	0.268
...median [IQR]	30.00 [18.95, 47.48]	31.94 [17.50, 50.14]	-0.059	28.41 [15.61, 43.95]	22.44 [11.87, 35.15]	0.208	28.75 (33.24)	23.60 (24.59)	0.176
Business Type									
...Commercial; n (%)	312 (86.0%)	835 (79.4%)	0.007	NA	NA	NA	NA	NA	NA
...Medicare; n (%)	51 (14.0%)	216 (20.6%)	-0.016	NA	NA	NA	NA	NA	NA
Insurance Plan Type									
...Comprehensive; n (%)	NA	NA	NA	188 (14.2%)	494 (6.5%)	0.024	NA	NA	NA
...HMO; n (%)	NA	NA	NA	150 (11.3%)	1,357 (18.0%)	-0.018	NA	NA	NA
...PPO; n (%)	NA	NA	NA	758 (57.2%)	4,103 (54.4%)	0.004	NA	NA	NA
...Others; n (%)	NA	NA	NA	229 (17.3%)	1,595 (21.1%)	-0.009	NA	NA	NA
SABA; n (%)	164 (45.2%)	615 (58.5%)	-0.019	773 (58.3%)	4,829 (64.0%)	-0.007	937 (55.5%)	5,444 (63.3%)	-0.159
SAMA; n (%)	16 (4.4%)	33 (3.1%)	0.007	60 (4.5%)	254 (3.4%)	0.006	076 (4.5%)	287 (3.3%)	0.062
SABA/SAMA; n (%)	25 (6.9%)	45 (4.3%)	0.011	118 (8.9%)	263 (3.5%)	0.022	143 (8.5%)	308 (3.6%)	0.207
ICS; n (%)	332 (91.5%)	442 (42.1%)	0.061	1,211 (91.4%)	4,052 (53.7%)	0.044	1,543 (91.4%)	4,494 (52.3%)	0.965
LABA without formoterol; n (%)	21 (5.8%)	3 (0.3%)	0.032	73 (5.5%)	57 (0.8%)	0.026	094 (5.6%)	060 (0.7%)	0.283
LAMA; n (%)	46 (12.7%)	70 (6.7%)	0.019	187 (14.1%)	378 (5.0%)	0.029	233 (13.8%)	448 (5.2%)	0.297
LABA/ICS without mometasone-formoterol; n (%)	91 (25.1%)	430 (40.9%)	-0.028	326 (24.6%)	3,189 (42.2%)	-0.031	417 (24.7%)	3,619 (42.1%)	-0.375
Blood eosinophilia test ; n (%)	0 (0.0%)	5 (0.5%)	-0.010	4 (0.3%)	15 (0.2%)	0.002	004 (0.2%)	020 (0.2%)	0.000
Serum immunoglobulin E (IgE) level test; n (%)	7 (1.9%)	28 (2.7%)	-0.005	29 (2.2%)	293 (3.9%)	-0.010	036 (2.1%)	321 (3.7%)	-0.095
H2 blocker; n (%)	5 (1.4%)	27 (2.6%)	-0.008	44 (3.3%)	311 (4.1%)	-0.004	049 (2.9%)	338 (3.9%)	-0.055
Oxygen codes; n (%)	11 (3.0%)	15 (1.4%)	0.011	40 (3.0%)	46 (0.6%)	0.018	051 (3.0%)	061 (0.7%)	0.171
Respiratory arrest/dependence on oxygen; n (%)	8 (2.2%)	6 (0.6%)	0.014	10 (0.8%)	25 (0.3%)	0.007	018 (1.1%)	031 (0.4%)	0.081

Aetion link to Optum results: https://bwh-dope.aetion.com/projects/details/1659/rwrs/68458
Aetion link to Marketscan results: https://bwh-dope.aetion.com/projects/details/1658/rwrs/68457

Appendix B

PS-matched									
	Optum			Marketscan			POOLED		
Variable	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.	Formoterol fumarate 10 mcg	Mometasone furoate/formoterol fumarate	St. Diff.
Number of patients	**165**	**165**		**919**	**919**		**1,084**	**1,084**	
Year of Cohort Entry Date									
...2010; n (%)	11 (6.7%)	7 (4.2%)	0.0107	73 (7.9%)	89 (9.7%)	-0.0061	084 (7.7%)	096 (8.9%)	-0.044
...2011; n (%)	33 (20.0%)	41 (24.8%)	-0.0102	276 (30.0%)	247 (26.9%)	0.0058	309 (28.5%)	288 (26.6%)	0.043
...2012; n (%)	40 (24.2%)	43 (26.1%)	-0.0038	210 (22.9%)	223 (24.3%)	-0.0029	250 (23.1%)	266 (24.5%)	-0.033
...2013; n (%)	34 (20.6%)	25 (15.2%)	0.0128	131 (14.3%)	136 (14.8%)	-0.0013	165 (15.2%)	161 (14.9%)	0.008
...2014; n (%)	28 (17.0%)	26 (15.8%)	0.0030	140 (15.2%)	131 (14.3%)	0.0023	168 (15.5%)	157 (14.5%)	0.028
...2015; n (%)	15 (9.1%)	16 (9.7%)	-0.0020	76 (8.3%)	78 (8.5%)	-0.0007	091 (8.4%)	094 (8.7%)	-0.011
...2016; n (%)	4 (2.4%)	7 (4.2%)	-0.0099	13 (1.4%)	15 (1.6%)	-0.0016	017 (1.6%)	022 (2.0%)	-0.030
...2017; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	000 (0.0%)	000 (0.0%)	#DIV/0!
...2018; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	0 (0.0%)	0 (0.0%)	#DIV/0!	000 (0.0%)	000 (0.0%)	#DIV/0!
...2019; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	NA	NA	NA	NA	NA	NA
...2020; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	NA	NA	NA	NA	NA	NA
Age*									
...mean (sd)	52.62 (15.47)	53.08 (16.38)	-0.0289	53.73 (15.97)	53.63 (17.30)	0.0060	53.56 (15.90)	53.55 (17.16)	0.001
...median [IQR]	54.00 [45.00, 63.50]	54.00 [44.00, 63.50]	0.0000	57.00 [45.00, 63.00]	56.00 [44.00, 64.00]	0.0601	56.54 (15.90)	55.70 (17.16)	0.051
Age categories									
...12-17; n (%)	4 (2.4%)	7 (4.2%)	-0.0099	32 (3.5%)	52 (5.7%)	-0.0103	036 (3.3%)	059 (5.4%)	-0.103
...18-39; n (%)	27 (16.4%)	23 (13.9%)	0.0064	114 (12.4%)	120 (13.1%)	-0.0020	141 (13.0%)	143 (13.2%)	-0.006
...40 - 64; n (%)	95 (57.6%)	100 (60.6%)	-0.0039	580 (63.1%)	540 (58.8%)	0.0055	675 (62.3%)	640 (59.0%)	0.068
...>= 65; n (%)	39 (23.6%)	35 (21.2%)	0.0051	193 (21.0%)	207 (22.5%)	-0.0032	232 (21.4%)	242 (22.3%)	-0.022
Geographic Region*									
...Northeast; n (%)	22 (13.3%)	19 (11.5%)	0.0051	225 (24.5%)	227 (24.7%)	-0.0004	247 (22.8%)	246 (22.7%)	0.002
...South; n (%)	68 (41.2%)	71 (43.0%)	-0.0028	293 (31.9%)	294 (32.0%)	-0.0002	361 (33.3%)	365 (33.7%)	-0.008
...Midwest; n (%)	44 (26.7%)	42 (25.5%)	0.0024	213 (23.2%)	206 (22.4%)	0.0017	257 (23.7%)	248 (22.9%)	0.019
...West; n (%)	31 (18.8%)	33 (20.0%)	-0.0027	172 (18.7%)	176 (19.2%)	-0.0011	203 (18.7%)	209 (19.3%)	-0.015
...Unknown/Missing; n (%)	NA	NA	NA	16 (1.7%)	16 (1.7%)	0.0000	NA	NA	NA
Metropolitan Statistical Area*									
...Urban; n (%)	NA	NA	NA	742 (80.7%)	763 (83.0%)	-0.0026	NA	NA	NA
...Rural; n (%)	NA	NA	NA	2 (0.2%)	5 (0.5%)	-0.0051	NA	NA	NA
...Unknown/Missing; n (%)	NA	NA	NA	175 (19.0%)	151 (16.4%)	0.0062	NA	NA	NA
General Health Related Measures									
Alcohol/Drug abuse or dependence ; n (%)	3 (1.8%)	2 (1.2%)	0.0049	9 (1.0%)	12 (1.3%)	-0.0028	012 (1.1%)	014 (1.3%)	-0.018
Obesity or Overweight; n (%)*	15 (9.1%)	20 (12.1%)	-0.0092	77 (8.4%)	87 (9.5%)	-0.0037	092 (8.5%)	107 (9.9%)	-0.048
Obesity; n (%)	13 (7.9%)	17 (10.3%)	-0.0080	68 (7.4%)	77 (8.4%)	-0.0036	081 (7.5%)	094 (8.7%)	-0.044
Overweight; n (%)	2 (1.2%)	3 (1.8%)	-0.0049	12 (1.3%)	10 (1.1%)	0.0018	014 (1.3%)	013 (1.2%)	0.009
Cardiovascular Measures									
Hypertension; n (%)*	63 (38.2%)	60 (36.4%)	0.0030	325 (35.4%)	332 (36.1%)	-0.0012	388 (35.8%)	392 (36.2%)	-0.008
Hyperlipidemia; n (%)*	54 (32.7%)	49 (29.7%)	0.0054	254 (27.6%)	273 (29.7%)	-0.0039	308 (28.4%)	322 (29.7%)	-0.029
MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)*	12 (7.3%)	9 (5.5%)	0.0071	75 (8.2%)	83 (9.0%)	-0.0027	087 (8.0%)	092 (8.5%)	-0.018
Old MI; n (%)	2 (1.2%)	1 (0.6%)	0.0063	5 (0.5%)	4 (0.4%)	0.0015	007 (0.6%)	005 (0.5%)	0.014
Acute MI; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	2 (0.2%)	2 (0.2%)	0.0000	002 (0.2%)	002 (0.2%)	0.000
Stable angina; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	10 (1.1%)	7 (0.8%)	0.0031	010 (0.9%)	007 (0.6%)	0.035
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	12 (7.3%)	9 (5.5%)	0.0071	68 (7.4%)	72 (7.8%)	-0.0015	080 (7.4%)	081 (7.5%)	-0.004
History of CABG or PTCA; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	7 (0.8%)	5 (0.5%)	0.0037	007 (0.6%)	005 (0.5%)	0.014
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)*	2 (1.2%)	3 (1.8%)	-0.0049	12 (1.3%)	9 (1.0%)	0.0028	014 (1.3%)	012 (1.1%)	0.018
Stroke (Ischemic or hemorrhagic); n (%)	2 (1.2%)	0 (0.0%)	0.0155	7 (0.8%)	6 (0.7%)	0.0012	009 (0.8%)	006 (0.6%)	0.024
TIA; n (%)	0 (0.0%)	2 (1.2%)	-0.0155	6 (0.7%)	3 (0.3%)	0.0057	006 (0.6%)	005 (0.5%)	0.014
Late effects of cerebrovascular disease; n (%)	0 (0.0%)	1 (0.6%)	-0.0110	5 (0.5%)	1 (0.1%)	0.0073	005 (0.5%)	002 (0.2%)	0.051
Atrial fibrillation and Other cardiac dysrhythmia; n (%)*	10 (6.1%)	12 (7.3%)	-0.0046	64 (7.0%)	62 (6.7%)	0.0011	074 (6.8%)	074 (6.8%)	0.000
Atrial fibrillation; n (%)	3 (1.8%)	6 (3.6%)	-0.0110	38 (4.1%)	32 (3.5%)	0.0031	041 (3.8%)	038 (3.5%)	0.016
Other cardiac dysrhythmia; n (%)	7 (4.2%)	8 (4.8%)	-0.0028	39 (4.2%)	39 (4.2%)	0.0000	046 (4.2%)	047 (4.3%)	-0.005
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)*	23 (13.9%)	25 (15.2%)	-0.0034	130 (14.1%)	126 (13.7%)	0.0011	153 (14.1%)	151 (13.9%)	0.006

Appendix B

Diabetes mellitus without mention of complications; n (%)	23 (13.9%)	25 (15.2%)	-0.0034	124 (13.5%)	119 (12.9%)	0.0017	147 (13.6%)	144 (13.3%)	0.009
Diabetes with specified complications; n (%)	4 (2.4%)	7 (4.2%)	-0.0099	29 (3.2%)	20 (2.2%)	0.0061	033 (3.0%)	027 (2.5%)	0.031
Diabetes with unspecified complications; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	5 (0.5%)	3 (0.3%)	0.0032	005 (0.5%)	003 (0.3%)	0.032
GI Conditions									
GERD; n (%)*	22 (13.3%)	28 (17.0%)	-0.0095	120 (13.1%)	123 (13.4%)	-0.0008	142 (13.1%)	151 (13.9%)	-0.023
Upper GI (Diseases of esophagus, stomach and duodenum including GERD) ; n (%)	25 (15.2%)	31 (18.8%)	-0.0087	152 (16.5%)	161 (17.5%)	-0.0024	177 (16.3%)	192 (17.7%)	-0.037
GI bleeding; n (%)*	3 (1.8%)	2 (1.2%)	0.0049	14 (1.5%)	12 (1.3%)	0.0017	017 (1.6%)	014 (1.3%)	0.025
Non-infective enteritis and colitis; n (%)	6 (3.6%)	10 (6.1%)	-0.0114	40 (4.4%)	37 (4.0%)	0.0020	046 (4.2%)	047 (4.3%)	-0.005
Intraoperative and postprocedural complications and disorders of digestive system; n (%)	2 (1.2%)	2 (1.2%)	0.0000	16 (1.7%)	17 (1.8%)	-0.0008	018 (1.7%)	019 (1.8%)	-0.008
Disorders of gallbladder, biliary tract and pancreas; n (%)*	1 (0.6%)	0 (0.0%)	0.0110	11 (1.2%)	7 (0.8%)	0.0040	012 (1.1%)	007 (0.6%)	0.054
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)*	2 (1.2%)	3 (1.8%)	-0.0049	17 (1.8%)	14 (1.5%)	0.0023	019 (1.8%)	017 (1.6%)	0.015
Osteoarthrosis; n (%)*	21 (12.7%)	22 (13.3%)	-0.0017	90 (9.8%)	91 (9.9%)	-0.0003	111 (10.2%)	113 (10.4%)	-0.007
Other rheumatic disorders (including gout); n (%)*	40 (24.2%)	46 (27.9%)	-0.0073	234 (25.5%)	249 (27.1%)	-0.0031	274 (25.3%)	295 (27.2%)	-0.043
Gout and other crystal arthropathies; n (%)	2 (1.2%)	4 (2.4%)	-0.0089	14 (1.5%)	20 (2.2%)	-0.0051	016 (1.5%)	024 (2.2%)	-0.052
Other rheumatic disorders; n (%)	38 (23.0%)	43 (26.1%)	-0.0063	225 (24.5%)	233 (25.4%)	-0.0018	263 (24.3%)	276 (25.5%)	-0.028
Neuro Conditions*									
Alzheimer and other Dementia Disease ; n (%)	1 (0.6%)	2 (1.2%)	-0.0063	7 (0.8%)	11 (1.2%)	-0.0040	008 (0.7%)	013 (1.2%)	-0.052
Seizure disorders (epilepsy); n (%)	0 (0.0%)	1 (0.6%)	-0.0110	6 (0.7%)	8 (0.9%)	-0.0022	006 (0.6%)	009 (0.8%)	-0.024
Delirium/Psychosis; n (%)	1 (0.6%)	1 (0.6%)	0.0000	8 (0.9%)	9 (1.0%)	-0.0010	009 (0.8%)	010 (0.9%)	-0.011
Other Conditions									
Hypothyroidism; n (%)*	12 (7.3%)	13 (7.9%)	-0.0022	99 (10.8%)	110 (12.0%)	-0.0036	111 (10.2%)	123 (11.3%)	-0.036
Chronic kidney disease stages I-III; n (%)*	4 (2.4%)	4 (2.4%)	0.0000	15 (1.6%)	19 (2.1%)	-0.0037	019 (1.8%)	023 (2.1%)	-0.022
Chronic kidney disease stages IV-V, ESRD; n (%)	1 (0.6%)	2 (1.2%)	-0.0063	7 (0.8%)	10 (1.1%)	-0.0031	008 (0.7%)	012 (1.1%)	-0.042
COPD; n (%)*	25 (15.2%)	29 (17.6%)	-0.0059	147 (16.0%)	160 (17.4%)	-0.0034	172 (15.9%)	189 (17.4%)	-0.040
Obstructive sleep apnea; n (%)*	15 (9.1%)	17 (10.3%)	-0.0039	108 (11.8%)	117 (12.7%)	-0.0026	123 (11.3%)	134 (12.4%)	-0.034
Syncope; n (%)	3 (1.8%)	2 (1.2%)	0.0049	12 (1.3%)	16 (1.7%)	-0.0033	015 (1.4%)	018 (1.7%)	-0.024
Falls; n (%)	1 (0.6%)	4 (2.4%)	-0.0147	5 (0.5%)	3 (0.3%)	0.0032	006 (0.6%)	007 (0.6%)	0.000
VTE; n (%)*	3 (1.8%)	4 (2.4%)	-0.0041	14 (1.5%)	9 (1.0%)	0.0045	017 (1.6%)	013 (1.2%)	0.034
Combined comorbidity score, 365 days*									
...mean (sd)	1.26 (1.30)	1.34 (1.15)	-0.0652	1.38 (1.39)	1.42 (1.52)	-0.0275	1.36 (1.38)	1.41 (1.47)	-0.035
...median [IQR]	1.00 [1.00, 1.00]	1.00 [1.00, 2.00]	0.0000	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.0000	1.00 (1.38)	1.00 (1.47)	0.000
Frailty Score: Empirical Version 365 days as Categories*									
...< 0.1 non frail; n (%)	81 (49.1%)	90 (54.5%)	-0.0075	409 (44.5%)	406 (44.2%)	0.0005	490 (45.2%)	496 (45.8%)	-0.012
...0.1 - < 0.2 prefrail; n (%)	45 (27.3%)	39 (23.6%)	0.0073	261 (28.4%)	261 (28.4%)	0.0000	306 (28.2%)	300 (27.7%)	0.011
... > 0.2 frail; n (%)	39 (23.6%)	36 (21.8%)	0.0038	249 (27.1%)	252 (27.4%)	-0.0006	288 (26.6%)	288 (26.6%)	0.000
Medication Use									
Use of oral corticosteroids; n (%)*	82 (49.7%)	79 (47.9%)	0.0026	458 (49.8%)	475 (51.7%)	-0.0027	540 (49.8%)	554 (51.1%)	-0.026
Use of antidepressants; n (%)*	40 (24.2%)	36 (21.8%)	0.0050	223 (24.3%)	228 (24.8%)	-0.0010	263 (24.3%)	264 (24.4%)	-0.002
Use of anticonvulsants; n (%)*	17 (10.3%)	15 (9.1%)	0.0039	101 (11.0%)	100 (10.9%)	0.0003	118 (10.9%)	115 (10.6%)	0.010
Use of beta blocker OR calcium channel blocker; n (%)*	24 (14.5%)	17 (10.3%)	0.0119	166 (18.1%)	164 (17.8%)	0.0007	190 (17.5%)	181 (16.7%)	0.021
Use of PPIs; n (%)*	37 (22.4%)	39 (23.6%)	-0.0025	267 (29.1%)	263 (28.6%)	0.0009	304 (28.0%)	302 (27.9%)	0.002
Use of opioids; n (%)*	37 (22.4%)	42 (25.5%)	-0.0063	245 (26.7%)	235 (25.6%)	0.0022	282 (26.0%)	277 (25.6%)	0.009
Use of antipsychotics; n (%)*	2 (1.2%)	1 (0.6%)	0.0063	16 (1.7%)	17 (1.8%)	-0.0008	018 (1.7%)	018 (1.7%)	0.000
Use of anxiolytics/hypnotics; n (%)*	15 (9.1%)	15 (9.1%)	0.0000	84 (9.1%)	96 (10.4%)	-0.0042	099 (9.1%)	111 (10.2%)	-0.037
Use of dementia meds; n (%)*	0 (0.0%)	1 (0.6%)	-0.0110	6 (0.7%)	9 (1.0%)	-0.0033	006 (0.6%)	010 (0.9%)	-0.035
Use of antiparkinsonian meds; n (%)*	2 (1.2%)	3 (1.8%)	-0.0049	23 (2.5%)	25 (2.7%)	-0.0012	025 (2.3%)	028 (2.6%)	-0.019
Use of Benzodiazepine; n (%)*	13 (7.9%)	15 (9.1%)	-0.0041	137 (14.9%)	139 (15.1%)	-0.0005	150 (13.8%)	154 (14.2%)	-0.012
All antidiabetic medications; n (%)*	17 (10.3%)	20 (12.1%)	-0.0054	109 (11.9%)	100 (10.9%)	0.0030	126 (11.6%)	120 (11.1%)	0.016
ACEI/ARB; n (%)*	48 (29.1%)	40 (24.2%)	0.0095	269 (29.3%)	256 (27.9%)	0.0026	317 (29.2%)	296 (27.3%)	0.042
Use of Anticoagulants; n (%)*	3 (1.8%)	5 (3.0%)	-0.0077	36 (3.9%)	33 (3.6%)	0.0015	039 (3.6%)	038 (3.5%)	0.005
Use of Amiodarone; n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	4 (0.4%)	6 (0.7%)	-0.0040	004 (0.4%)	006 (0.6%)	-0.028
Digoxin; n (%)	1 (0.6%)	1 (0.6%)	0.0000	9 (1.0%)	10 (1.1%)	-0.0010	010 (0.9%)	011 (1.0%)	-0.010
Use of Diuretics; n (%)*	38 (23.0%)	31 (18.8%)	0.0092	215 (23.4%)	215 (23.4%)	0.0000	253 (23.3%)	246 (22.7%)	0.014
Use of Aspirin; n (%)	1 (0.6%)	0 (0.0%)	0.0110	7 (0.8%)	7 (0.8%)	0.0000	008 (0.7%)	007 (0.6%)	0.012
NSAIDs (NOT including aspirin); n (%)	18 (10.9%)	24 (14.5%)	-0.0101	115 (12.5%)	145 (15.8%)	-0.0088	133 (12.3%)	169 (15.6%)	-0.095
HRT (Use of estrogens, progestins, androgens); n (%)*	19 (11.5%)	19 (11.5%)	0.0000	122 (13.3%)	128 (13.9%)	-0.0016	141 (13.0%)	147 (13.6%)	-0.018
Use of Statins ; n (%)*	45 (27.3%)	46 (27.9%)	-0.0011	262 (28.5%)	280 (30.5%)	-0.0037	307 (28.3%)	326 (30.1%)	-0.040

Appendix B

Healthcare Utilization Measures									
Use of any drugs claims*									
...mean (sd)	28.42 (20.68)	28.33 (20.78)	0.0043	28.80 (20.50)	29.10 (20.30)	-0.0147	28.74 (20.53)	28.98 (20.37)	-0.012
...median [IQR]	22.00 [13.00, 40.00]	21.00 [14.00, 36.00]	0.0482	24.00 [14.00, 38.00]	25.00 [15.00, 38.00]	-0.0490	23.70 (20.53)	24.39 (20.37)	-0.034
Number of office visits*									
...mean (sd)	11.42 (9.14)	11.35 (9.38)	0.0076	12.04 (9.09)	12.12 (9.09)	-0.0088	11.95 (9.10)	12.00 (9.13)	-0.005
...median [IQR]	9.00 [5.00, 15.00]	8.00 [5.00, 13.50]	0.1080	10.00 [5.00, 16.00]	10.00 [6.00, 15.00]	0.0000	9.85 (9.10)	9.70 (9.13)	0.016
Number of ED visits*									
...mean (sd)	0.41 (0.86)	0.38 (1.00)	0.0322	0.52 (1.28)	0.49 (1.20)	0.0242	0.50 (1.23)	0.47 (1.17)	0.025
...median [IQR]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.0000	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.0000	0.00 (1.23)	0.00 (1.17)	0.000
Number of hospitalizations*									
...mean (sd)	0.04 (0.23)	0.05 (0.27)	-0.0399	0.39 (2.13)	0.34 (1.75)	0.0257	0.34 (1.96)	0.30 (1.62)	0.022
...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 (1.96)	0.00 (1.62)	0.000
Recent hospitalization (-30 days to Index Rx date); n (%)	0 (0.0%)	0 (0.0%)	#DIV/0!	11 (1.2%)	12 (1.3%)	-0.0009	011 (1.0%)	012 (1.1%)	-0.010
Old hospitalizations (-365 to -31 days); n (%)	15 (9.1%)	11 (6.7%)	0.0085	97 (10.6%)	93 (10.1%)	0.0016	112 (10.3%)	104 (9.6%)	0.023
Number of Pulmonologist/Allergist visits*									
...mean (sd)	0.10 (0.45)	0.08 (0.43)	0.0454	1.61 (3.53)	1.79 (3.40)	-0.0519	1.38 (3.26)	1.53 (3.14)	-0.047
...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]	-0.2885	0.00 (3.26)	0.85 (3.14)	-0.266
Pulmonologist /allergist on CED; n (%)*	2 (1.2%)	2 (1.2%)	0.0000	117 (12.7%)	136 (14.8%)	-0.0057	119 (11.0%)	138 (12.7%)	-0.053
Number of hospital days*									
...mean (sd)	0.23 (1.38)	0.45 (3.12)	-0.0912	0.39 (2.13)	0.34 (1.75)	0.0257	0.37 (2.03)	0.36 (2.02)	0.005
...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 (2.03)	0.00 (2.02)	0.000
Occurrence of basic or comprehensive metabolic blood chemistry test; n (%)*	58 (35.2%)	60 (36.4%)	-0.0020	290 (31.6%)	286 (31.1%)	0.0009	348 (32.1%)	346 (31.9%)	0.004
Number of HbA1C test ordered*									
...mean (sd)	0.42 (0.88)	0.56 (1.23)	-0.1309	0.42 (0.95)	0.39 (0.92)	0.0321	0.42 (0.94)	0.42 (0.97)	0.000
...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 (0.94)	0.00 (0.97)	0.000
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)*	3 (1.8%)	6 (3.6%)	-0.0110	49 (5.3%)	57 (6.2%)	-0.0038	052 (4.8%)	063 (5.8%)	-0.045
Number of Mammograms (Breast cancer screening); n (%)*	21 (12.7%)	22 (13.3%)	-0.0017	131 (14.3%)	142 (15.5%)	-0.0031	152 (14.0%)	164 (15.1%)	-0.031
Number of Pap smear (Cervical cancer screening); n (%)*	14 (8.5%)	14 (8.5%)	0.0000	88 (9.6%)	78 (8.5%)	0.0037	102 (9.4%)	092 (8.5%)	0.032
Flu vaccine; n (%)*	29 (17.6%)	27 (16.4%)	0.0029	139 (15.1%)	144 (15.7%)	-0.0015	168 (15.5%)	171 (15.8%)	-0.008
Pneumococcal vaccine; n (%)*	7 (4.2%)	8 (4.8%)	-0.0028	37 (4.0%)	37 (4.0%)	0.0000	044 (4.1%)	045 (4.2%)	-0.005
Copay for pharmacy cost (charges in U.S. $)*									
...mean (sd)	36.76 (34.33)	35.41 (28.84)	0.0426	32.44 (29.37)	32.24 (28.07)	0.0070	33.10 (30.17)	32.72 (28.19)	0.013
...median [IQR]	28.33 [18.09, 45.06]	29.38 [17.97, 48.77]	-0.0331	27.29 [14.61, 42.08]	27.00 [16.00, 41.79]	0.0101	27.45 (30.17)	27.36 (28.19)	0.003
Business Type*									
...Commercial; n (%)	140 (84.8%)	136 (82.4%)	0.0026	NA	NA	NA	NA	NA	NA
...Medicare; n (%)	25 (15.2%)	29 (17.6%)	-0.0059	NA	NA	NA	NA	NA	NA
Insurance Plan Type*									
...Comprehensive; n (%)	NA	NA	NA	96 (10.4%)	96 (10.4%)	0.0000	NA	NA	NA
...HMO; n (%)	NA	NA	NA	111 (12.1%)	102 (11.1%)	0.0029	NA	NA	NA
...PPO; n (%)	NA	NA	NA	543 (59.1%)	551 (60.0%)	-0.0012	NA	NA	NA
...Others; n (%)	NA	NA	NA	169 (18.4%)	170 (18.5%)	-0.0002	NA	NA	NA
SABA; n (%)*	87 (52.7%)	86 (52.1%)	0.0008	555 (60.4%)	540 (58.8%)	0.0021	642 (59.2%)	626 (57.7%)	0.030
SAMA; n (%)*	6 (3.6%)	7 (4.2%)	-0.0030	38 (4.1%)	42 (4.6%)	-0.0024	044 (4.1%)	049 (4.5%)	-0.020
SABA/SAMA; n (%)*	6 (3.6%)	8 (4.8%)	-0.0059	52 (5.7%)	50 (5.4%)	0.0013	058 (5.4%)	058 (5.4%)	0.000
ICS; n (%)*	138 (83.6%)	137 (83.0%)	0.0007	813 (88.5%)	805 (87.6%)	0.0010	951 (87.7%)	942 (86.9%)	0.024
LABA without formoterol; n (%)*	2 (1.2%)	3 (1.8%)	-0.0049	31 (3.4%)	33 (3.6%)	-0.0011	033 (3.0%)	036 (3.3%)	-0.017
LAMA; n (%)*	16 (9.7%)	15 (9.1%)	0.0020	106 (11.5%)	114 (12.4%)	-0.0026	122 (11.3%)	129 (11.9%)	-0.019
LABA/ICS without mometasone-formoterol; n (%)*	54 (32.7%)	55 (33.3%)	-0.0010	253 (27.5%)	266 (28.9%)	-0.0026	307 (28.3%)	321 (29.6%)	-0.029
Blood eosinophilia test ; n (%)*	0 (0.0%)	0 (0.0%)	#DIV/0!	3 (0.3%)	3 (0.3%)	0.0000	003 (0.3%)	003 (0.3%)	0.000
Serum immunoglobulin E (IgE) level test; n (%)*	2 (1.2%)	2 (1.2%)	0.0000	26 (2.8%)	33 (3.6%)	-0.0045	028 (2.6%)	035 (3.2%)	-0.036
H2 blocker; n (%)*	4 (2.4%)	2 (1.2%)	0.0089	33 (3.6%)	32 (3.5%)	0.0005	037 (3.4%)	034 (3.1%)	0.017
Oxygen codes; n (%)*	4 (2.4%)	5 (3.0%)	-0.0037	16 (1.7%)	14 (1.5%)	0.0016	020 (1.8%)	019 (1.8%)	0.000
Respiratory arrest/dependence on oxygen; n (%)*	0 (0.0%)	1 (0.6%)	-0.0110	6 (0.7%)	6 (0.7%)	0.0000	006 (0.6%)	007 (0.6%)	0.000

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