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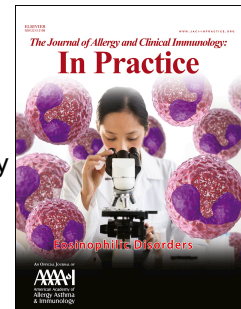
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Treatment patterns and disease burden associated with multiple-inhaler triple-therapy use in asthma

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Abstract**Background:**

Addition of a long-acting muscarinic antagonist (LAMA) is recommended for patients with asthma uncontrolled on inhaled corticosteroid/long-acting β_2 -agonist (ICS/LABA) therapy. This is the first large-scale, real-world study examining multiple-inhaler triple-therapy (MITT) use in asthma.

Objective: To describe real-world prevalence, outcomes and treatment patterns associated with MITT.

Methods: This retrospective cohort study used medical and pharmacy claims from the Optum Research Database. Patients were diagnosed with asthma between January 01, 2013–July 31, 2018 with evidence of MITT use (≥ 1 overlapping days' supply of ICS, LABA and LAMA). Annual MITT prevalence (primary endpoint) was assessed in the prevalent population; eligible patients were ≥ 18 years with ≥ 2 asthma diagnoses during the study period, and continuous enrollment for the entire year. Secondary outcomes (adherence [proportion of days covered [PDC]], MITT persistence, healthcare resource utilization [HCRU], costs) were assessed in the incident MITT population; eligible patients were ≥ 18 years, with ≥ 2 asthma diagnoses and continuous enrollment during both the 12-month baseline and 12-month follow-up periods. Patients with chronic obstructive pulmonary disease or cystic fibrosis were excluded.

Results: MITT prevalence was low but increased from 0.35% (95% confidence interval [CI]: 0.32, 0.37) in 2014/2015 to 1.00% (95% CI: 0.96, 1.04) in 2017/2018. Among 1,831 incident MITT users there was a substantial disease burden, demonstrated by high HCRU and exacerbation rates. Adherence and persistence to MITT was low (mean [SD] PDC: 0.31 [0.27]) and 12% (n=216) remained on MITT 12 months post-initiation.

Conclusions: Overall, MITT use among patients with asthma is low. Patients initiating MITT have substantial disease burden and significant unmet needs.

Highlights box**1. What is already known about this topic?**

At the time this study was conducted, single inhaler therapies were not routinely available for asthma. Up until that point, triple therapy was administered via multiple inhalers (MITT). However, very little is still known about prevalence and treatment patterns associated with MITT in real-world clinical practice.

2. What does this article add to our knowledge?

Prevalence of MITT use is low in real-world practice, but increased marginally over the study period. New users of MITT have a substantial disease burden and unmet needs.

3. How does this study impact current management guidelines?

Our study indicates that more needs to be done to improve the care of patients with uncontrolled asthma, including improvements in implementation of current guidelines, and better use of existing and emerging therapeutic strategies.

Key words

Asthma, multiple-inhaler, triple therapy, disease burden, treatment patterns, claims database, real-world data, medication adherence

Abbreviations

Agency for Healthcare Research and Quality, AHRQ; Confidence interval, CI; Chronic obstructive pulmonary disease, COPD; Eosinophil, EOS; Emergency room, ER; Global Initiative for Asthma, GINA; General practitioner, GP; Healthcare resource utilization, HCRU; Health insurance portability and accountability, HIPAA; International Classification of Diseases, ICD; Inhaled corticosteroid, ICS; Immunoglobulin E, IgE; Interleukin-5, IL-5; Long-acting β_2 -agonist, LABA; Long-acting muscarinic antagonist, LAMA; Medicare Advantage with Part D, MAPD; Multiple-inhaler triple therapy, MITT; Optum Research Database, ORD; Proportion of days covered, PDC; Phosphodiesterase, PDE; Short-acting β_2 -agonist, SABA; Short-acting muscarinic-antagonist, SAMA; Standard deviation, SD.

Introduction

Asthma is a chronic inflammatory airway disease, characterized by reversible airway limitation and a range of debilitating symptoms from cough and wheeze to dyspnea and exacerbations, which can, in severe cases, be life-threatening.¹ These symptoms can have a negative impact on the quality of life of patients with asthma, with more severe disease phenotypes generally associated with poorer quality of life, higher healthcare resource utilization (HCRU) and greater costs.^{1, 2} For example, although patients with severe asthma account for $\leq 10\%$ of the total asthma population, approximately 50% of all annual asthma-related healthcare costs can be attributed to this group.^{3, 4}

It is estimated that approximately 334 million people worldwide⁵ and around 25 million people in the US⁶ currently suffer from asthma. The annual total cost of asthma in the US was estimated at approximately \$81.9 billion in 2013,⁷ of which, 61% was related to direct medical costs (prescription costs, hospital-based outpatient visits, emergency room (ER) visits, inpatient stays) with the remainder due to absenteeism and mortality;⁷ it is likely that this cost has continued to increase in the intervening period. Currently, it is estimated that 40–60% of patients have poorly controlled asthma based on real-world studies.⁸⁻¹⁰ Yet, despite attempts to optimize adherence to inhaled corticosteroids in combination with a long-acting β_2 -agonist (ICS/LABA), asthma remains poorly controlled in an estimated 30–50% of patients,^{6, 11-13} highlighting unmet clinical needs, and a significant health and economic burden for both patients and society. Indeed, a recent study projected that the total economic burden associated with uncontrolled asthma (defined by poor symptom control, limitations in daily activity and/or increased exacerbations) will rise to almost \$1 trillion over the next 20 years among American adolescents and adults.¹⁴

The Global Initiative for Asthma (GINA) report recommends adding a long-acting muscarinic antagonist (LAMA) as an additional controller for GINA Step 4/5 patients with uncontrolled asthma who are currently receiving medium-to-high dose ICS/LABA maintenance therapy as supported by the NAEPP asthma management guidelines.^{1, 15} In a clinical trial setting, the addition of a LAMA to ICS/LABA maintenance therapy as part of a multiple-inhaler triple-therapy (MITT) regimen has been shown to improve lung function and reduce the risk of severe exacerbations among patients with asthma.¹⁶ However, multiple-inhaler regimens introduce an added complexity to dosing, which may negatively impact patient adherence.^{18, 19} Therefore, the current study aimed to address the paucity of real-world evidence on MITT use by utilizing claims data from a large asthma patient population to evaluate the prevalence and patterns of MITT use (e.g. adherence and persistence to MITT), as well as reporting on the rate of exacerbations, HCRU and associated costs among MITT users diagnosed with asthma in a real-world setting.

Methods

Study design

This was a retrospective cohort study including commercially insured enrollees and Medicare Advantage with Part D (MAPD) beneficiaries diagnosed with asthma between January 01, 2013 and July 31, 2018 (study period; **Figure 1**). Medical and pharmacy data, and enrollment information were obtained from the Optum Research Database (ORD), an adjudicated, de-identified, and health insurance portability and accountability (HIPAA)-compliant research database. Relevant laboratory data (e.g. blood eosinophil [EOS] counts) were included for the subset of patients with laboratory results available in the claims and/or electronic health record data. The managed healthcare plans in the ORD include patients across a wide geographic distribution in the US and the database is generally representative of the US Medicare and commercially insured populations.

Eligibility criteria

Full inclusion and exclusion criteria for primary and secondary outcomes are listed in **Table E1** and associated ICD 9/10 codes can be found in **Tables E2 and E3**. For the primary outcome of MITT prevalence (MITT defined as ≥ 1 day of overlap in the days' supply of all three triple therapy components [i.e. ICS+LABA+LAMA] based on pharmacy fill dates), patients were required to have ≥ 2 asthma diagnoses on different dates from one or more physicians (based on ICD 9/10 codes in **Table E2**), be ≥ 18 years as of the year of the asthma diagnosis, and have continuous enrollment for the 12-month period. A subgroup of patients was additionally required to have ≥ 1 pharmacy claim for an ICS-containing medication during the same year as continuous enrollment. For secondary outcomes evaluated among incident MITT users, the baseline period was defined as the 12 months prior to, and including (unless otherwise stated), the index date (the first date with all three MITT components between January 01, 2014 and July 31, 2017). The 12 months following the index date was defined as the follow-up period. Patients were required to be ≥ 18 years old as of the index date, have ≥ 2 asthma diagnoses (≥ 1 in the baseline period and ≥ 1 in the follow-up period), and have continuous enrollment during the baseline and follow-up periods.

Exclusion criteria included a diagnosis of COPD, cystic fibrosis, acute respiratory failure, or lung cancer in any position during the baseline or follow-up periods, as well as unknown age, gender, geographic region or insurance type. Patients with evidence of MITT use in the baseline period (excluding the index date) were also excluded from the incident MITT population.

Study objectives

The primary objective was to describe the annual prevalence of MITT use between 01 August, 2014 and 31 July, 2018 among patients diagnosed with asthma (overall population) and in a subset of patients diagnosed with asthma and treated with an ICS-containing medication during the baseline period, prior to MITT initiation (baseline-ICS treated population). Secondary objectives were to describe demographics, clinical characteristics, asthma-related HCRU, exacerbations, costs and MITT treatment patterns (adherence, persistence and treatment discontinuation) during baseline and/or follow-up periods among asthma patients initiating MITT.

Endpoints

Sociodemographic and clinical information was assessed for incident MITT users at index date (age, gender, ethnicity), during the baseline period (Agency for Healthcare Research and Quality [AHRQ]-defined comorbidities (based on ICD-9-CM and ICD-10 codes as described in **Table E3**), maintenance medication, treatment regimen immediately preceding MITT initiation), or in the baseline and follow-up periods (exacerbation rates and exacerbation-related costs, EOS counts, rescue medication use). The numeric value of the first, last, highest and average EOS laboratory results were captured. Respiratory medication use was captured from national drug codes on pharmacy claims at the medication class level. Use of systemic corticosteroids was identified as at least one systemic corticosteroid prescription during the 12 month baseline period. This could be prescribed for low-dose maintenance use, or for acute use following an asthma-related exacerbation; detailed analysis of systemic corticosteroid use was not conducted.

Exacerbation rates were reported for asthma exacerbations overall and separately for hospitalization-defined exacerbations (i.e. hospitalization with asthma diagnosis in the primary position at any time during hospitalization), ER-defined exacerbations (i.e. ER visit with an asthma diagnosis code in the primary position), and steroid-defined exacerbations (a medical claim with an asthma diagnosis in the primary position plus an average daily dose of ≥ 20 mg of prednisone [or equivalent] for 3–28 days based on pharmacy claims, or an injectable steroid claim [medical or pharmacy] within ± 7 days of the medical claim).

Exacerbation-related costs were calculated for asthma exacerbations overall and separately by site of care as the sum of asthma-related medical and pharmacy costs within the exacerbation episode. Among patients with an exacerbation, exacerbation-related costs were presented as an average cost per exacerbation.

All-cause and asthma-related HCRU and costs were calculated during the baseline and follow-up periods for ambulatory visits (i.e. physician offices and hospital outpatient settings), urgent care visits, ER visits and inpatient admissions, and were defined as asthma-related if the claim included an asthma diagnosis in the primary position or if the claim was for an asthma treatment.

To assess treatment adherence, overall proportion of days covered (PDC) was calculated during the follow-up period by dividing the number of days on which medication (ICS+LABA+LAMA) was available by the number of days between the index date and the end of the follow-up period. To measure the PDC for the individual components of MITT, the number of days with medication (i.e. the number of days with an ICS-containing medication, a LABA-containing medication, or a LAMA-containing medication) was divided by the number of days between the index date and the end of the follow-up period. Patients who were fully adherent had a PDC of 1.0, while PDC <1.0 indicated reduced adherence.

Discontinuation of any component of MITT in the follow-up period was defined as a treatment gap of >45 days after the earliest runout date for one or more components of the MITT regimen based on pharmacy claims, while persistence with triple therapy was measured as the days to discontinuation and the total number of prescription fills for each component of MITT prior to discontinuation. Switching between drugs within drug classes was allowed, and these cases were not considered to be discontinuations.

Statistical analyses

For the primary outcome, the number of eligible patients, the number of patients treated with MITT and the annual prevalence of MITT use (including 95% confidence intervals [CI]) are reported. Estimates of MITT prevalence are presented for the overall population and for the baseline ICS-treated population. All variables for secondary outcomes were analyzed descriptively, using numbers and percentages for categorical variables, and means, medians and standard deviations (SD) for continuous variables. Kaplan–Meier analysis was used to estimate the time to discontinuation of MITT and includes the censored-adjusted percentage of patients who persisted on MITT at pre-specified periods of interest and median time to discontinuation. Costs are presented by medication adherence (PDC $\geq$ 0.8: adherent; PDC <0.8: non-adherent). No statistical comparisons were performed.

Results

Annual prevalence of MITT use among asthma patients

Figure E1 details the patient identification and attrition among asthma patients and the baseline ICS treated population in the baseline period. The number of patients meeting study selection criteria increased in each year over the four 12-month periods between 1 August 2014 and 31 July 2018. Annual prevalence of MITT use was low, but increased during the study period for the overall population. In the most recent year, the prevalence of MITT use among the overall population was 1.00% (95% CI: 0.96, 1.04; n=2,534), and 2.63% (95% CI: 2.53, 2.73; n=2,510) among the ICS-treated patients (**Figure 2**).

Sociodemographic, clinical characteristics and HCRU among incident MITT users during the baseline period

A total of 1,831 patients who initiated MITT (hereafter referred to as MITT initiators) were identified during the study period. This cohort had a mean (SD) age of 56.1 (14.4) years, two-thirds were female and approximately half were White/Caucasian (**Table I**). Overall, more than two-thirds of incident MITT users had commercial insurance with the remainder being Medicare Advantage with Part D enrollees. Based on the index pharmacy claim, 31% of patients were prescribed MITT by pulmonologists, 26% by allergists, and 24% by primary care practitioners (**Table I**).

The majority of incident MITT users had additional comorbidities, including cardiovascular disease (52.3%), and AHRQ-defined hypertension (49.2%), hypercholesterolemia (45.0%), obesity (25.9%) and diabetes (19.7%) (**Table I**). Of the 33.9% of incident MITT users with an EOS measurement in the baseline period, approximately two-thirds had counts ≥ 150 cells/ μ L, with 42% having counts ≥ 300 cells/ μ L (**Table I**). Ninety percent of MITT initiators (n=1,655) were receiving asthma maintenance treatment in the 45 days immediately prior to MITT initiation (**Table E4**) with 69% using an ICS/LABA combination, 62% using leukotriene modifiers, 22% using ICS, and 16% using LAMA alone during the baseline period (**Table I**). Approximately 4% (n=78) of patients were using anti-immunoglobulin E biologic therapy prior to MITT initiation (**Table I**). The vast majority of patients initiated MITT using a fixed-dose combination of ICS/LABA with add-on LAMA (85%) at index date (**Figure E2**). Rescue medication use was high in the baseline period prior to MITT initiation, with 83% of patients using SABA and 89% using systemic corticosteroids (**Table I**).

During the baseline period, 46% of incident MITT users had ≥ 1 exacerbation, equivalent to a mean annualized rate of 0.75 (95% CI: 0.71, 0.79) (**Table II**). Approximately 40% had ≥ 1 steroid-defined

exacerbation, 8% had ≥ 1 ER visit-defined exacerbation, and 4% had ≥ 1 hospitalization-defined exacerbation (**Table II**). Total mean (SD) asthma-related per patient exacerbation costs were \$2,660 (6,148) and \$13,941 (13,369) for hospitalization-defined exacerbations (**Table II**). All incident MITT users had an all-cause ambulatory visit in the baseline period, with ~84% having an asthma-related ambulatory visit (**Table III**). Mean (SD) asthma-related annual total (medical + pharmacy) healthcare costs per patient equated to \$4,558 (8,527) (**Table III**).

Adherence and persistence with MITT in the follow-up period

Overall adherence to MITT was low, with a mean (SD) PDC of 0.31 (0.27) (**Figure 3**). However, adherence to individual components of the triple regimen was higher, with mean (SD) PDC of 0.54 (0.29), 0.53 (0.30) and 0.41 (0.31) for ICS-, LABA- and LAMA-containing therapies, respectively (**Figure 3**).

The rate of triple therapy discontinuation at 12 months post-treatment initiation was high, with only 51% (n=1,383) remaining on MITT after 30 days; while 12% remained on MITT (n=216), 19% remained on ICS-containing medication (n=299), and just 10% remained on LAMA-containing medication (n=169) at 12 months (**Figure 4**). Median time to discontinuation was 43 days.

All-cause, asthma-related and exacerbation-related healthcare costs by treatment adherence during the 12-month follow-up period

Mean (SD) total all-cause medical costs per patient were numerically higher among patients with lower adherence to MITT (PDC < 0.8 ; n=1,669) compared to patients with higher adherence (PDC ≥ 0.8 ; n=162), at \$14,918 (28,074) versus \$13,459 (19,462), respectively. Asthma-related and all-cause inpatient costs per patient were numerically higher among patients with lower adherence to MITT versus those who were adherent (\$474 [4,768] versus \$146 [1,860], and \$2,882 [16,175] versus \$1,111 [5,328], respectively) (**Figure 5A**). Not surprisingly, pharmacy costs tended to be numerically higher among patients with greater adherence to MITT, compared to those with lower adherence (\$16,556 [14,619] versus \$8,885 [13,093]) (**Figure 5B**).

The total mean (SD) asthma-related costs per patient for any type of exacerbation were all numerically greater among patients with lower adherence to MITT compared to costs for adherent patients (\$4,061 [10,106] versus \$2,152 [3,882]), while the total asthma-related cost of a hospitalization or ER-defined exacerbation was \$10,729 (17,215) for patients with lower adherence to MITT compared to \$7,724 (9,227) among adherent patients (**Figure 6**).

Discussion

Prevalence of MITT use among this real-world study population was low but steadily increased each year (from 0.35% in 2014 to 1.00% in 2018). The initial low uptake of MITT could be attributed to the fact that while LAMAs were available for the treatment of COPD, they were not approved for the treatment of patients with asthma at the start of the study period and therefore, US treatment guidelines had not yet been updated to include the use of a LAMA for patients with asthma uncontrolled on ICS/LABA. The GINA report did not recommend the use of a LAMA (tiotropium) as a Step 4 add-on treatment until 2016.

Asthma patients prescribed MITT in our study had a substantial disease burden and unmet needs, demonstrated by high HCRU, costs of care, comorbidity burden, and use of rescue medications, including a notably high rate of systemic steroid use. This reflects the nature of the population included in this study, as patients requiring triple therapy are more likely to have significantly uncontrolled disease. Therefore, the subsequent use of systemic corticosteroids would be expected to be high. Furthermore, 85% of patients reported ≥ 1 asthma-related ambulatory visit during the baseline period, with mean baseline total asthma-related costs per patient per year of \$4,558. Exacerbation rates among MITT users also indicate a large disease burden and poorly controlled asthma: almost half (46.3%) of MITT users had ≥ 1 exacerbation of any severity in the baseline period, substantially higher than the exacerbation rate of 12.5% reported among the general US asthma population and similar to the rate for severe asthma patients at GINA Steps 4/5 (45.5%) reported in a recent study.²⁰ These findings are not unexpected given that 90% of patients within our study initiated MITT as a step-up from their current treatment suggesting a substantial pre-existing disease burden and unmet clinical needs among this population. Indeed, 85% of patients in this study initiated step-up therapy from ICS/LABA, in line with the GINA-recommended guidelines for patients with poorly controlled asthma. We observed that 16% of MITT initiators had previously used LAMA alone during the baseline period. While we acknowledge this could indicate potential misclassification of the study population with patients with either COPD or asthma-COPD overlap (ACO), this is unlikely due to the robust nature of our inclusion and exclusion criteria (i.e., a diagnosis of COPD in the baseline or follow-up periods would have resulted in exclusion from the study population). Overall, it is likely that the relatively high rate of unopposed LAMA use in asthma is a true reflection of clinical practice at the time this study was conducted.

Despite this burden, overall adherence to MITT was low (mean PDC: 0.3), but was higher when individual components of the MITT regimen were evaluated separately, suggesting that patients may not have been consistently taking their medications at the same time and thus not receiving the

maximum benefit of all three components (ICS+LABA+LAMA) given together. Additionally, discontinuation rates from MITT were high, with only half of patients continuing MITT 30-days post-treatment initiation and only 12% of patients continuing MITT to the end of the follow-up period. While the reasons for poor adherence in this study are unknown, the complexities of using multiple inhalers with different devices and dosing regimens (e.g. once versus twice daily) reflect a substantial medication burden and may have made it difficult for patients to maintain adherence to MITT. Furthermore, it is possible that specific therapies were not adhered to because they provided no perceived benefit to the patient. For example, a recent study suggested that over 80% of patients with uncontrolled asthma had poor adherence to ICS/LABA prior to initiating a step-up in treatment, which could suggest dissatisfaction with their prior treatment regimen.²¹ Typically, poor adherence is associated with poorer asthma control and greater disease burden.^{22, 23} Indeed, results from this study suggest increased healthcare costs and asthma-related exacerbation costs among patients who were less adherent to MITT versus those with higher adherence, highlighting the unmet need for improved adherence among patients treated with MITT. As would be expected, the exception was pharmacy costs which were numerically higher among adherent patients. However, it should be noted, that no statistical comparisons were performed as the objective of this study was to describe the population.

Overall, the findings from this study illustrate a substantial disease and economic burden among patients with asthma who initiated MITT, yet adherence to medication was low, indicating clear unmet medical needs in this patient population. While single-inhaler triple-therapy has only recently been approved for the treatment of asthma,^{17, 24} at the time of this study triple therapy was delivered via multiple devices. Thus, poor adherence to MITT observed in our study may be attributed to complexities associated with multiple-inhaler use (e.g. different devices and dosing regimens). This may suggest that a more simplified inhaler regimen may benefit these patients, since once-daily versus twice-daily inhaled treatment has previously been shown to improve adherence in patients with asthma,^{25, 26} while administration via single versus multiple inhalers has also been shown to improve adherence and persistence in patients with COPD and asthma.^{18, 19}

Suzuki et al.²⁷ recently published a similar cohort study on patients initiating triple therapy. However, their study looked specifically at a population from Japan and included patients with asthma as well as asthma/COPD overlap. Similar to our study, the majority of patients were also on maintenance ICS/LABA medication before stepping up to MITT in a GINA-recommended step-wise fashion.¹ Adherence (measured by PDC and medication possession ratio) and continuation rates among patients from that study were generally higher than reported here, though discontinuation

was still high, with 38.5% of patients with asthma continuing MITT for ≥ 1 year, compared with 12% in our study.²⁷ It should be noted, however, that differences in healthcare systems may have contributed to the differences seen in the results of each study.

While 90% of patients in our study were on maintenance medication prior to initiating a step-up to a MITT regimen, a step-up approach may not benefit all patients. A more targeted treatment intervention based on specific disease traits that contribute to disease burden may be more beneficial. For example, 42% of incident MITT users in our study who had an EOS test at baseline (n=620) had a blood EOS count of ≥ 300 cells/ μ L, which is typically associated with a more severe disease phenotype.²⁸ While EOS counts have also been proposed as an indicator to predict response to ICS treatment, our data could provide additional insights into a personalized, multidimensional ‘treatable traits’ approach to asthma treatment, where EOS counts are used to identify patients likely to benefit from additional therapies, such as triple therapy with high- or low-dose ICS, increasing ICS dose²⁹ in dual therapy or using biologic therapy to target type 2 inflammation.^{17, 30, 31} A targeted, biomarker-directed treatable traits approach may help clinicians reach better informed treatment decisions, which in turn may encourage patients to become more adherent to treatment as well as offering a more economic/cost-effective approach to treating asthma by minimizing the use of expensive but ineffective treatments.

There are a number of limitations to our study that should be recognized. As adherence to multiple medications can be calculated in different ways, different calculations may result in different interpretation of treatment adherence. However, to mitigate this, we used two definitions of adherence to identify patients who were adherent to MITT overall and those who were adherent to individual components of the MITT regimen. Nevertheless, we cannot be certain if all patients took medication completely as prescribed; as adherence was based on pharmacy fills, we may have censored patients for discontinuation who were actually non-adherent but still on treatment. In addition, there is a chance that some patients skipped doses in order to save costs but did not permanently discontinue; to mitigate this, a treatment gap of 45 days was required to be classified as discontinuation. As with any claims-based study, missing data may have influenced interpretation. However, patients with missing demographic data (i.e. missing age, gender, geographic region, or insurance type) were excluded from the study. In addition, data presented are descriptive with no statistical testing performed for the comparisons reported. Finally, laboratory results (i.e. EOS counts) were only available from a relatively small subset of patients with an available test result, which may limit the generalizability of these data.

Despite these limitations, our study provides invaluable real-world data on MITT use and associated HCRU and costs from a very large data source representing a diverse population of patients with asthma across a wide geographic distribution, which may enable a degree of generalization to other populations.

Conclusion

MITT prevalence among patients diagnosed with asthma and those using ICS-containing medication was low but did appear to steadily increase over time during this study, though the introduction of single-inhaler triple therapies and widespread availability of biologic therapies is likely to temper this increase in clinical practice. The vast majority of MITT initiators had used asthma maintenance medication in the 45 days preceding the index date, but despite this, these patients still have a large disease and economic burden. Adherence and persistence to MITT were low, but adherence to each individual triple therapy component was demonstrably higher, suggesting that patients were not using all three MITT components simultaneously. Simplifying the inhaler regimen might improve adherence and persistence in patients with asthma who require triple therapy.

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Declarations

Ethics approval This retrospective study utilized de-identified insurance claims data, and as such, did not require institutional review board review and approval, or informed consent procedures.

Consent to participate N/A

Consent for publication N/A

Availability of data and material Information on GlaxoSmithKline's (GSK) data sharing commitments and requesting access to anonymized individual participant data and associated documents from GSK-sponsored studies can be found at www.clinicalstudydatarequest.com. The data reported in this publication are contained in a database owned by Optum which contains proprietary elements. Therefore, it cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third-parties assumes certain data security and privacy protocols are in place and that the third-parties have executed Optum's standard license agreement which includes restrictive covenants governing the use of the data.

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Tables

Table I. Sociodemographic and clinical characteristics among incident multiple-inhaler triple-therapy (MITT) users during the 12-month baseline period.

	Incident MITT users (N=1,831)
Age, mean (SD)	56.1 (14.4)
≥18–44 years, n (%)	383 (20.9)
45–64 years, n (%)	898 (49.0)
≥65 years, n (%)	550 (30.0)
Female, n (%)	1,221 (66.7)
Race/ethnicity, n (%)	
White/Caucasian	871 (47.6)
Black/African American	127 (6.9)
Hispanic	121 (6.6)
Asian	46 (2.5)
Other/unknown	666 (36.4)
Selected comorbidities*, n (%)	
Other lower respiratory disease [†]	1,365 (74.6)
Other upper respiratory disease	1,257 (68.7)
Allergic rhinitis	1,052 (57.5)
Cardiovascular disease [‡]	958 (52.3)
Hypertension	901(49.2)
Hypercholesterolemia	823 (45.0)
Obesity	474 (25.9)
Diabetes mellitus	360 (19.7)
Provider specialty[§] on index MITT claim , n (%)	
Pulmonologist	568 (31.0)
Allergist	477 (26.1)
Primary care/GP/Internist	443 (24.2)
Other specialty [¶]	153 (8.4)
Multiple specialties	13 (0.7)
No data available	177 (9.7)
Eosinophil test results[#] (n=620), n (%)	

<150 cells/ μ L	200 (32.3)
150 to <300 cells/ μ L	159 (25.7)
$\geq$ 300 cells/ μ L	261 (42.1)
Maintenance medication**	
ICS/LABA combination	1,254 (68.5)
Leukotriene modifier	1,142 (62.4)
ICS	394 (21.5)
LAMA	292 (16.0)
LABA	46 (2.5)
Methylxanthine	41 (2.2)
LAMA/LABA	28 (1.5)
Mast cell stabilizer	2 (0.1)
PDE-4 enzyme inhibitor	2 (0.1)
Biologics††, n (%)	
Anti-IgE	78 (4.3)
IL-5 inhibitors	2 (0.1)
Rescue medications††, n (%)	
SABA	1,514 (82.7)
SAMA	69 (3.8)
SABA/SAMA combination	205 (11.2)
Oral or injectable corticosteroids	1,635 (89.3)

*AHRQ-defined comorbidities (except for cardiovascular disease). Patients may have had more than one comorbidity.

†Including but not limited to: pulmonary fibrosis, respiratory bronchiolitis, pulmonary edema, lung transplant, breathing abnormalities, wheezing, sleep apnea, chest pain and coughing, as well as other disorders of the lungs and diaphragm. Excludes asthma or chronic obstructive pulmonary disease. ††The presence of one or more of the following conditions was classified as cardiovascular disease: arrhythmia. (atrial fibrillation or flutter), heart failure, coronary artery disease and myocardial infarction, cerebrovascular event (transient ischemic attack or stroke), or hypertension, and defined as $\geq$ 1 ICD-9-CM or ICD-10 diagnosis in any position.

§Provider specialty is based on the provider type for the last component(s) of triple therapy among patients with available data. Provider specialties for components of triple therapy prescribed prior to the index date are not included.

¶Includes all provider specialties other than Pulmonologist, Allergist, Primary Care/GP/Internist

#For the population with available laboratory results.

503 **Maintenance medication use was captured from pharmacy claims.

504 ^{††}Medical and pharmacy claims were used to identify biologic medications.

505 ^{§§}Rescue medication use was captured from pharmacy and medical claims.

506 AHRQ, Agency for Healthcare Research and Quality; GP, general practitioner; ICD, International Classification
507 of Diseases; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; LABA, long-acting β_2 -agonist;
508 LAMA, long-acting muscarinic antagonist; PDE, phosphodiesterase; SABA, short-acting β_2 -agonist; SAMA,
509 short-acting muscarinic-antagonist; SD, standard deviation.

Table II. Exacerbations and associated costs among incident multiple-inhaler triple-therapy (MITT) users during the 12-month baseline period.

	MITT users (N=1,831)
Any exacerbation*	
≥1 exacerbation, n (%)	848 (46.3)
Annual exacerbation rate, (95% CI)	0.75 (0.71, 0.79)
Total asthma-related per patient cost of exacerbations (\$), mean (SD)	2,660 (6,148)
Total cost per exacerbation (\$), mean (SD)	1,644 (4,193)
Steroid-defined exacerbation[†]	
≥1 exacerbation, n (%)	721 (39.4)
Annual exacerbation rate (95% CI)	0.60 (0.57, 0.64)
Total asthma-related per patient cost of exacerbations (\$), mean (SD)	1,168 (2,391)
Total cost per exacerbation (\$), mean (SD)	766 (1,307)
ER visit-defined exacerbation[‡]	
≥1 exacerbation, n (%)	151 (8.3)
Annual exacerbation rate (95% CI)	0.11 (0.09, 0.12)
Total asthma-related per patient cost of exacerbations (\$), mean (SD)	3,360 (4,785)
Total cost per exacerbation (\$), mean (SD)	2,550 (3,243)
Hospitalization-defined exacerbation[§]	
≥1 exacerbation, n (%)	65 (3.6)
Annual exacerbation rate (95% CI)	0.04 (0.03, 0.05)
Total asthma-related per patient cost of exacerbations (\$), mean (SD)	13,941 (13,369)
Total cost per exacerbation (\$), mean (SD)	12,246 (12,172)

*Exacerbations are classified according to the highest severity contributing event; identified during the pre-index period, including index date.

[†]Steroid-defined exacerbation: an average daily dose of ≥20 mg of prednisone (or equivalent) for 3–28 days based on pharmacy claims, or an injectable steroid based on medical or pharmacy claims, and an ambulatory (office or outpatient) visit with an asthma diagnosis in the primary position within ±7 days.

[‡]ER visit-defined exacerbation: an ER visit with an asthma diagnosis code in the primary position.

[§]Hospitalization-defined exacerbation: a hospitalization with an asthma diagnosis code in the primary position.

ER, emergency room; CI, confidence interval; SD, standard deviation

Table III. Healthcare resource utilization and costs among incident multiple-inhaler triple-therapy (MITT) users during the 12-month baseline period.

	MITT users (N=1,831)
All-cause	
All-cause HCRU, n (%)	
Ambulatory visit	1,831 (100.0)
Urgent care visit	88 (4.8)
ER visit	746 (40.7)
Hospitalizations	199 (10.9)
All-cause healthcare costs (\$)*	
Mean (SD)	
Total costs (medical + pharmacy)	19,003 (23,494)
Medical costs	12,337 (19,670)
Pharmacy costs	6,666 (10,435)
Median	
Total costs (medical + pharmacy)	10,949
Medical costs	5,810
Pharmacy costs	3,714
Asthma-related[†]	
Asthma-related HCRU, n (%)	
Ambulatory visit	1,547 (84.5)
Urgent care visit	21 (1.2)
ER visit	170 (9.3)
Hospitalization	65 (3.6)
Asthma-related healthcare costs (\$)†	
Mean (SD)	
Total costs (medical + pharmacy)	4,558 (8,527)
Medical costs	2,282 (7,602)
Pharmacy costs	2,276 (3,131)
Median	
Total costs (medical + pharmacy)	2,517

Medical costs	385
Pharmacy costs	1,690

*Costs were adjusted using the annual medical care component of the Consumer Price Index to 2018 dollars.

Utilization counts and costs are per patient per year.

[†]Asthma-related HCRU and costs were those for which the claim included an asthma diagnosis in the primary position or if the claim was for an asthma treatment.

ER; emergency room; HCRU, healthcare resource utilization; SD, standard deviation

Figures

Figure 1. Study design.

MITT, multiple-inhaler triple therapy.

Figure 2. Annual prevalence of multiple-inhaler triple-therapy (MITT) use among all eligible patients diagnosed with asthma.

Annual prevalence = number of patients treated with MITT during the year/number of eligible patients in the year.

ICS, inhaled corticosteroid.

Figure 3. Overall adherence (mean proportion of days covered [PDC]) for multiple-inhaler triple-therapy (MITT) and individual MITT components, among incident MITT users in the 12-month follow-up period.

Overall PDC: number of overlapping days with all three active ingredients (ICS + LABA + LAMA) divided by number of days between the index date through to the end of the 12-month follow-up period (12 months post-index date + 1 day)

Individual MITT component PDC: number of days with medication (eg, number of days with an ICS-containing, LABA-containing or LAMA-containing medication) divided by number of days between the index date and the end of the 12-month follow-up period.

Dashed line depicts threshold for adherence; <0.8, not adherent; ≥0.8, adherent.

ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

Figure 4. Time to treatment discontinuation among incident multiple-inhaler triple-therapy (MITT) users in the 12-month follow-up period.

This proportion is the same as the cumulative incidence rate. Discontinuation is defined as a treatment gap of >45 days after the runout date for each component of triple therapy. By definition, patients are not at risk to discontinue within the last 46 days of the follow-up period. Follow-up period is 12-months post-index date + 1 day.

ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist.

Figure 5. All-cause and asthma-related (A) medical costs and (B) pharmaceutical costs among incident multiple-inhaler triple-therapy (MITT) users in the 12-month follow-up period according to adherence (PDC).

PDC was defined as the number of days with all three MITT components on hand. Costs were given as per patient costs, and adjusted using the annual medical care component of the Consumer Price Index to 2018 dollars.

ER, emergency room; PDC, proportion of days covered; SD, standard deviation.

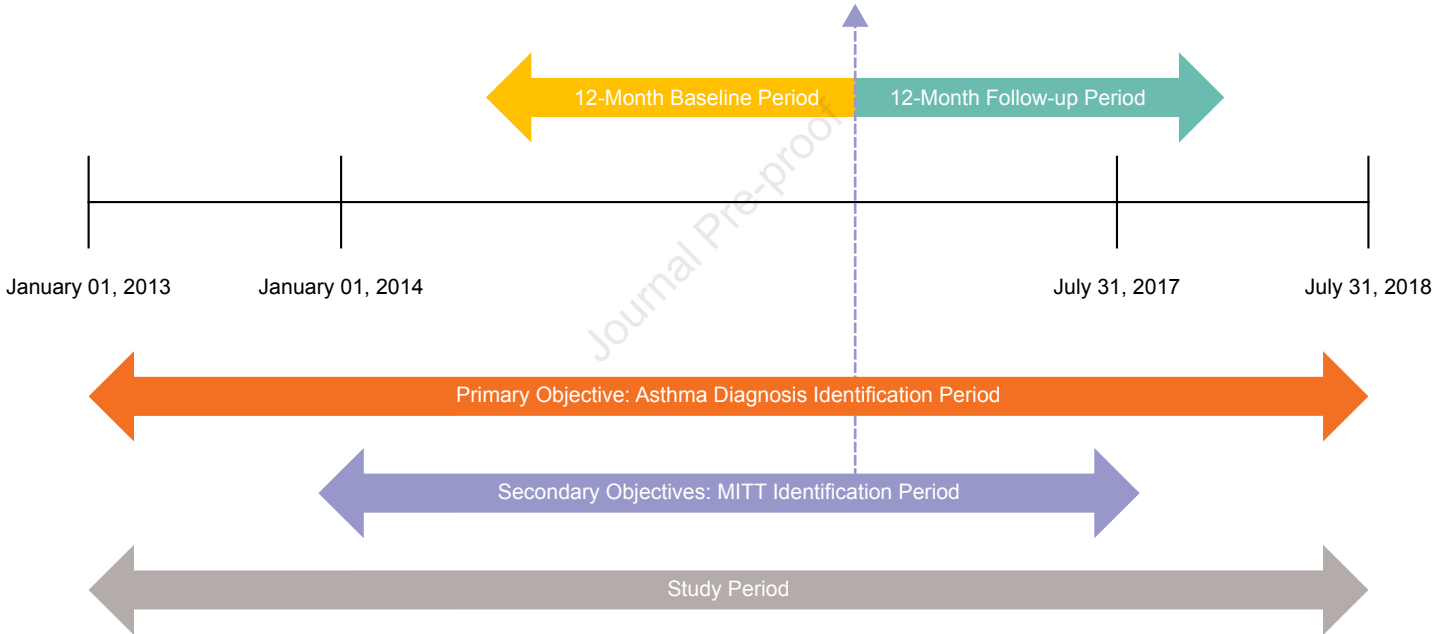
Figure 6. Asthma-related exacerbation costs by adherence among incident multiple-inhaler triple-therapy (MITT) users during the 12-month follow-up period.

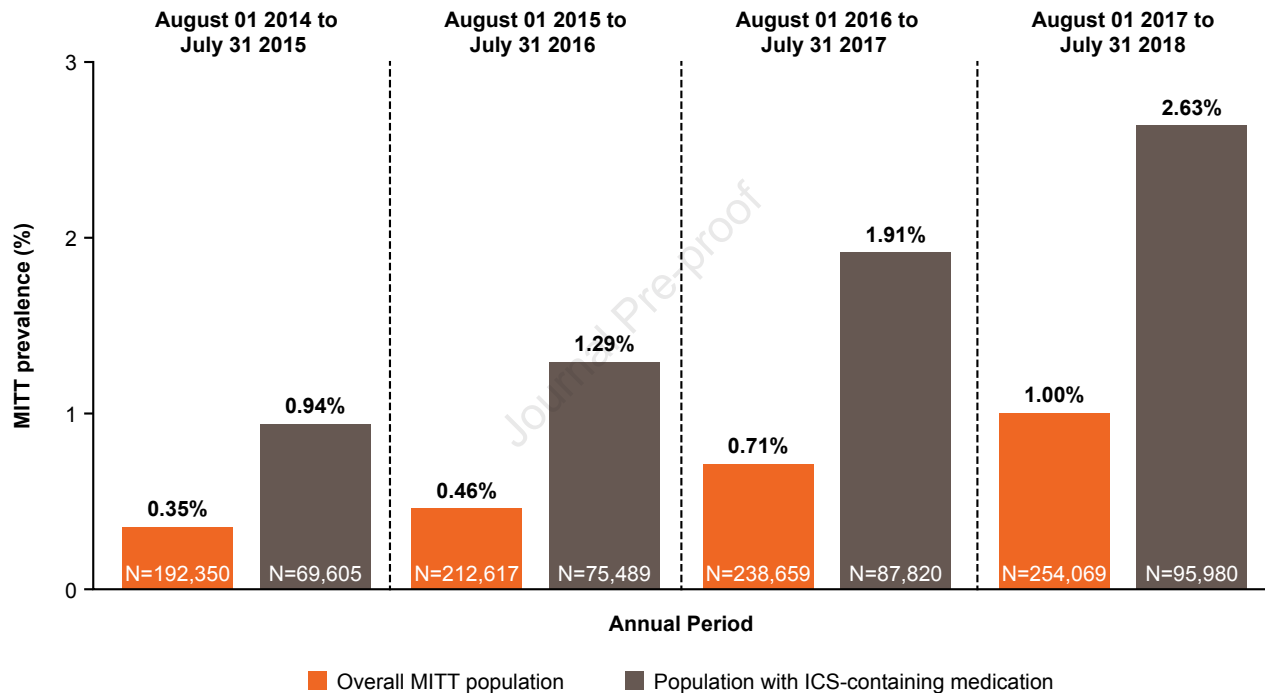
Follow-up period is 12 months post-index + 1 day. Asthma-related costs are presented for the subset of patients with any exacerbation (left) or a hospitalization or ER-visit defined exacerbation (right). Exacerbations are classified according to the highest severity contributing event.

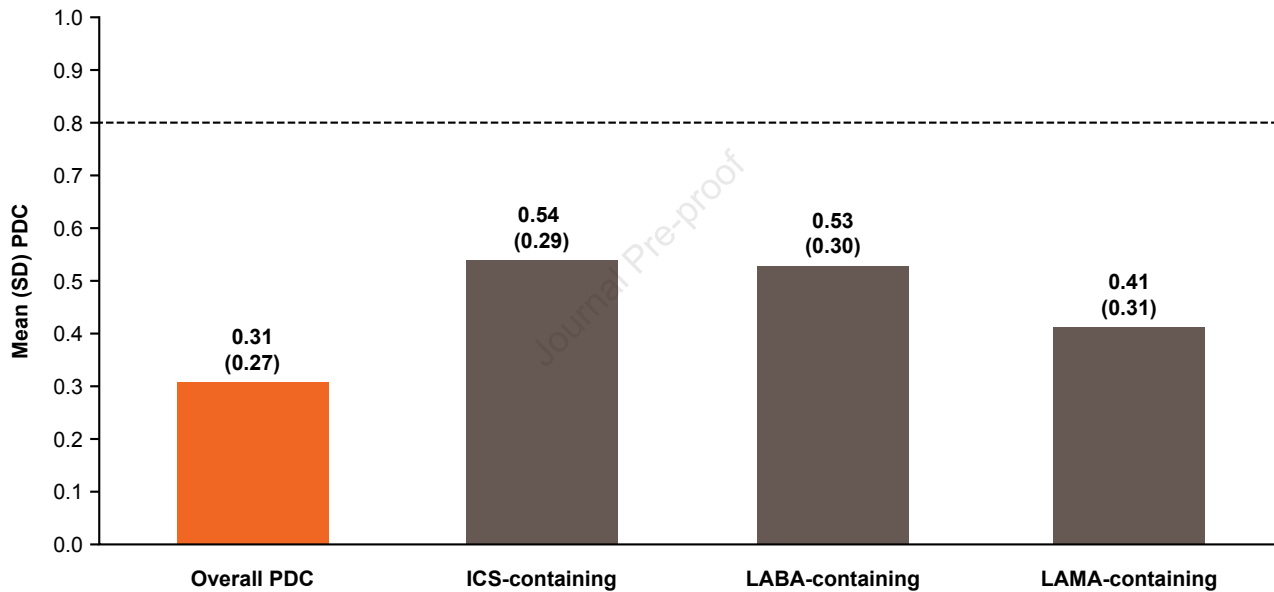
Any class of exacerbations: a hospitalization-defined exacerbation (a hospitalization with an asthma diagnosis code in the primary position), an ER visit-defined exacerbation (an ER visit with an asthma diagnosis code in the primary position), or a steroid-defined exacerbation (a medical claim with an asthma diagnosis in the primary position).

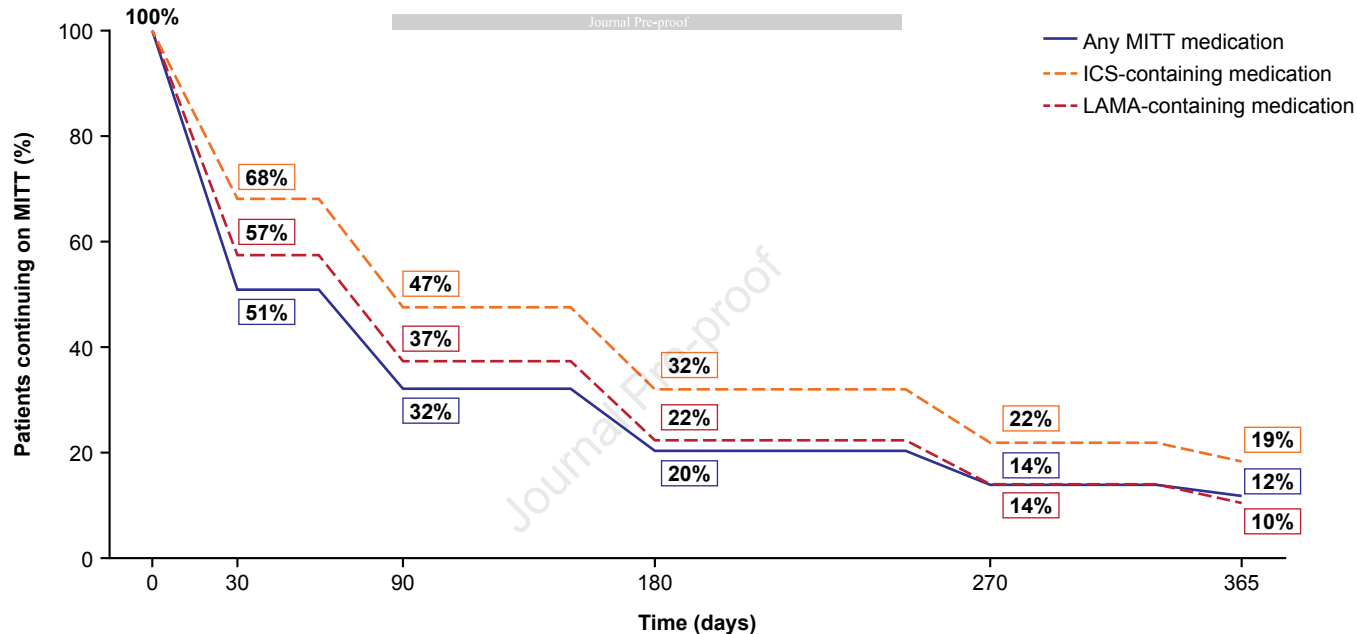
ER, emergency room; PDC, proportion of days covered; SD, standard deviation.

Index Date (secondary objectives):
*First date with all three triple
therapy components on hand*



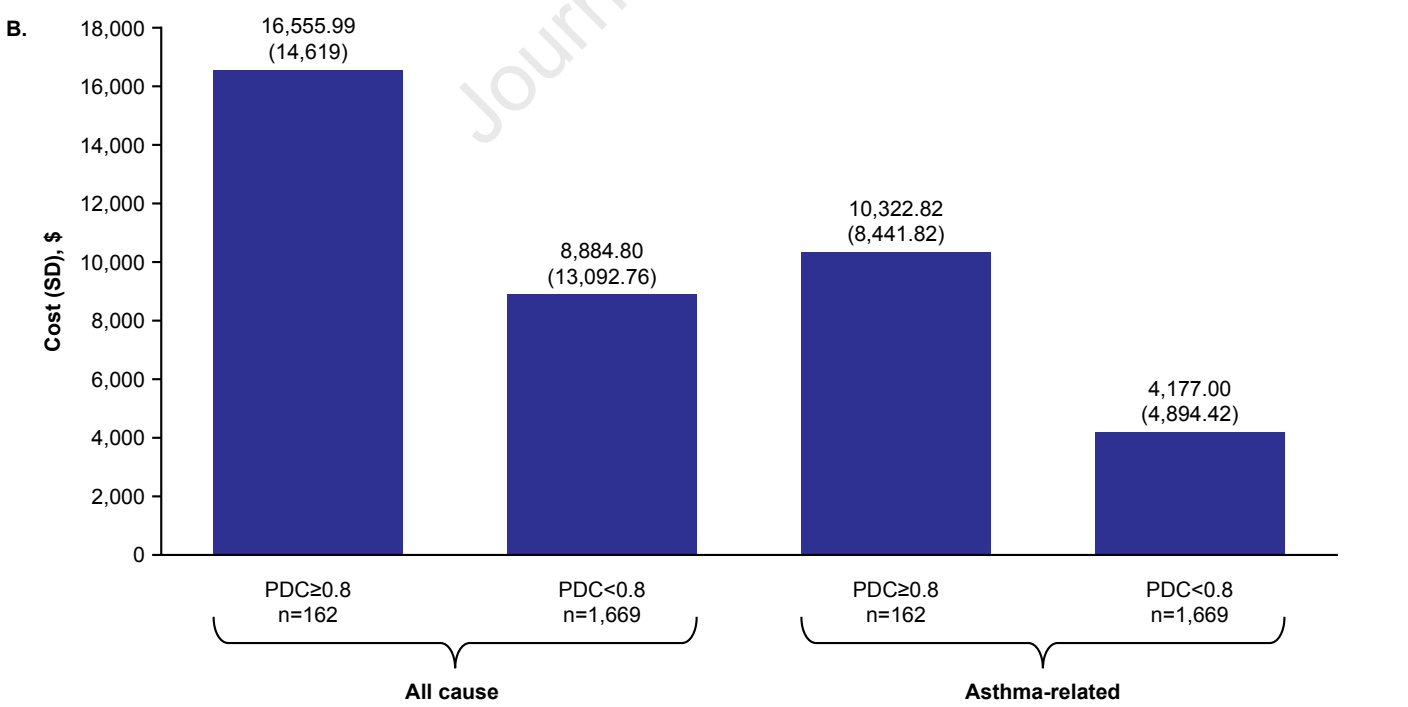
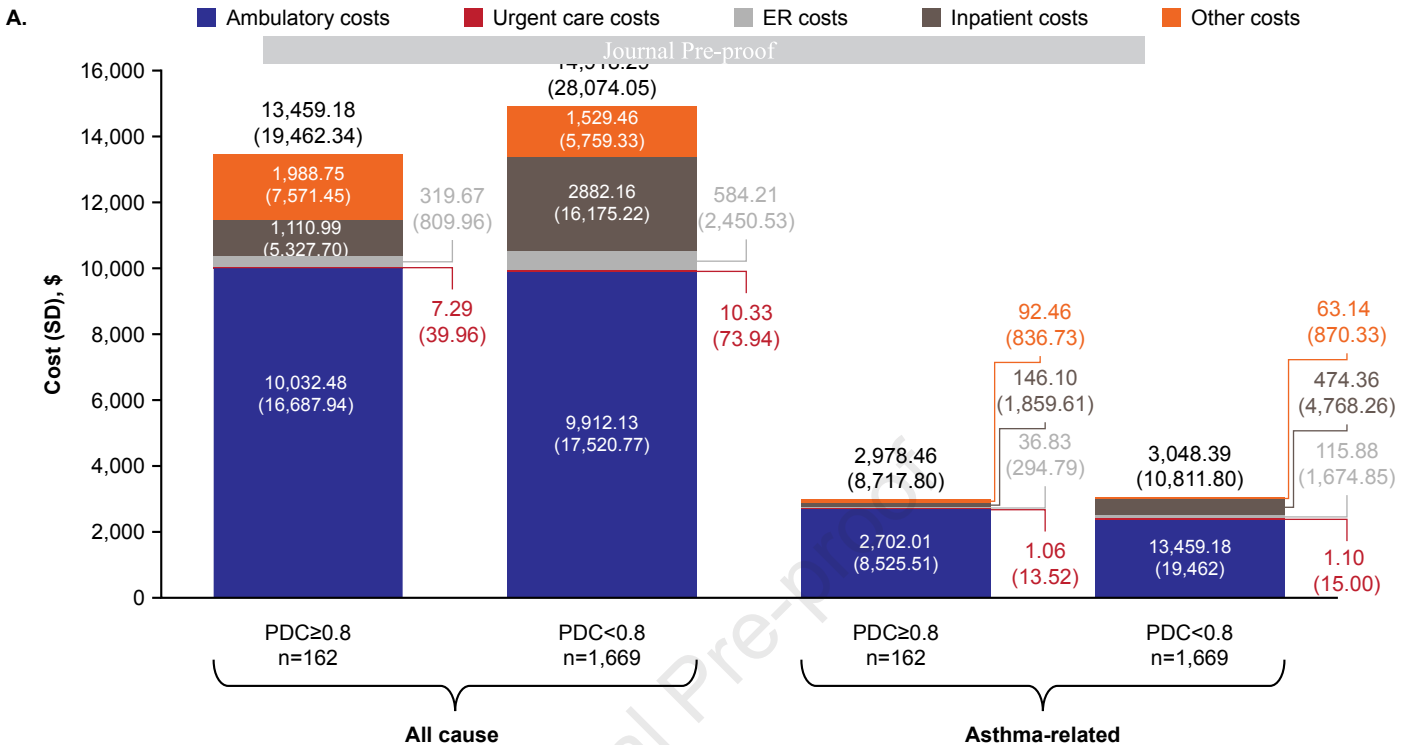


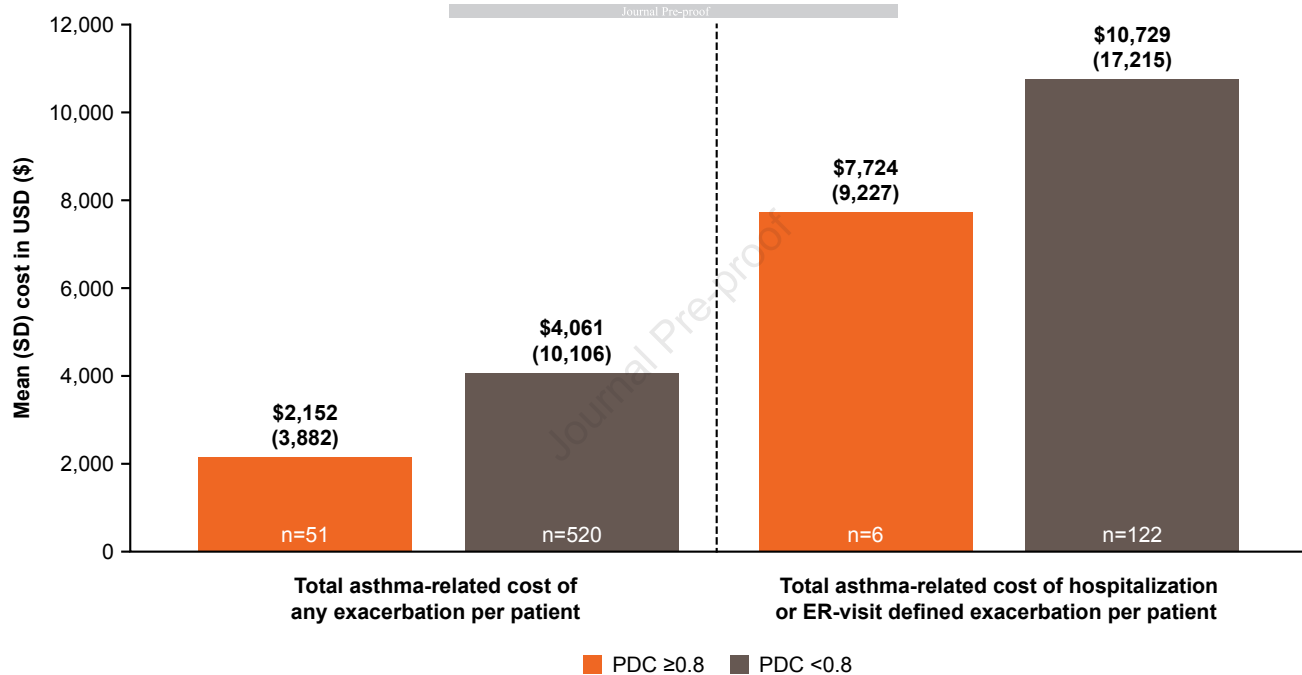




Number at risk

Any MITT medication	1,831	1,383	666	374	256	216
ICS-containing medication	1,615	1,392	839	520	356	299
LAMA-containing medication	1,615	1,440	678	364	227	169





SUPPLEMENTARY TABLES AND FIGURES

Table E1. Eligibility criteria for primary and secondary outcomes.

PRIMARY OUTCOME	
INCLUSION CRITERIA	EXCLUSION CRITERIA
• ≥ 2 asthma diagnoses in any position on different dates of service between January 01, 2013 and July 31, 2018. • ≥ 1 pharmacy claim for an ICS-containing medication between January 01, 2013 and July 31, 2018 (only for the analysis among patients with asthma treated with inhaled maintenance therapy). • For each year strata (eg, August 01, 2017 – July 31, 2018), patients were required to meet the following additional inclusion criteria: ○ ≥ 1 asthma diagnosis during the year ○ Age ≥ 18 years as of the year of the asthma diagnosis ○ ≥ 1 pharmacy claims for an ICS-containing medication during the year (only for the analysis among patients with asthma treated with ICS-containing medication) ○ Continuous enrollment with medical and pharmacy coverage for the entire year	• ≥ 1 COPD diagnosis in any position between January 01, 2013 and July 31, 2018. • ≥ 1 cystic fibrosis, acute respiratory failure, or lung cancer diagnosis in any position between January 01, 2013 and July 31, 2018. • Unknown age, gender, geographic region, or insurance type.
SECONDARY OUTCOMES	
INCLUSION CRITERIA	EXCLUSION CRITERIA
• Treatment with MITT (ie, ICS + LABA + LAMA). The index date was defined as the first date with all three triple therapy components between January 01, 2014 and July 31, 2017. • ≥ 1 asthma diagnosis in any position in the baseline period; the index date was included in the baseline period. • ≥ 1 asthma diagnosis in any position in the follow-up period; the index date was excluded from the follow-up period. • Age ≥ 18 years as of the year of the index date. • Continuous enrollment with medical and pharmacy coverage of 12 months in the baseline period and of 12 months in the follow-up period.	• Evidence of MITT in the baseline period prior to the index date. Patients with ≥ 1 day of overlap in the days' supply of all three triple therapy components in the baseline period were excluded. • ≥ 1 COPD diagnosis in any position in the baseline or follow-up periods. • ≥ 1 cystic fibrosis, acute respiratory failure, or lung cancer diagnosis in any position in the baseline or follow-up periods. • Unknown gender, geographic region, or insurance type.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy.

Table E2. International classification of disease (ICD) codes to identify asthma.

Code	Code Type	Description
493	ICD-9 Dx	Asthma
493.00	ICD-9 Dx	Extrinsic asthma, unspecified
493.01	ICD-9 Dx	Extrinsic asthma with status asthmaticus
493.02	ICD-9 Dx	Extrinsic asthma, with (acute) exacerbation
493.10	ICD-9 Dx	Intrinsic asthma, unspecified
493.11	ICD-9 Dx	Intrinsic asthma with status asthmaticus
493.12	ICD-9 Dx	Intrinsic asthma, with (acute) exacerbation
493.20	ICD-9 Dx	Chronic obstructive asthma, unspecified
493.21	ICD-9 Dx	Chronic obstructive asthma with status asthmaticus
493.22	ICD-9 Dx	Chronic obstructive asthma, with (acute) exacerbation
493.81	ICD-9 Dx	Exercise induced bronchospasm
493.82	ICD-9 Dx	Cough variant asthma
493.90	ICD-9 Dx	Asthma, unspecified, unspecified status
493.91	ICD-9 Dx	Asthma, unspecified with status asthmaticus
493.92	ICD-9 Dx	Asthma, unspecified, with (acute) exacerbation
J45	ICD-10 Dx	Asthma
J4520	ICD-10 Dx	Mild intermittent asthma, uncomplicated
J4521	ICD-10 Dx	Mild intermittent asthma with (acute) exacerbation
J4522	ICD-10 Dx	Mild intermittent asthma with status asthmaticus
J4530	ICD-10 Dx	Mild persistent asthma, uncomplicated
J4531	ICD-10 Dx	Mild persistent asthma with (acute) exacerbation
J4532	ICD-10 Dx	Mild persistent asthma with status asthmaticus
J4540	ICD-10 Dx	Moderate persistent asthma, uncomplicated
J4541	ICD-10 Dx	Moderate persistent asthma with (acute) exacerbation
J4542	ICD-10 Dx	Moderate persistent asthma with status asthmaticus
J4550	ICD-10 Dx	Severe persistent asthma, uncomplicated
J4551	ICD-10 Dx	Severe persistent asthma with (acute) exacerbation
J4552	ICD-10 Dx	Severe persistent asthma with status asthmaticus
J45901	ICD-10 Dx	Unspecified asthma with (acute) exacerbation
J45902	ICD-10 Dx	Unspecified asthma with status asthmaticus
J45909	ICD-10 Dx	Unspecified asthma, uncomplicated
J45990	ICD-10 Dx	Exercise induced bronchospasm
J45991	ICD-10 Dx	Cough variant asthma
J45998	ICD-10 Dx	Other asthma

Table E3. International classification of disease codes (ICD) to identify comorbidities.

Code	Code Type	Description
Chronic obstructive pulmonary disease		
491	ICD-9 Dx	Chronic bronchitis
491.0	ICD-9 Dx	Simple chronic bronchitis
491.1	ICD-9 Dx	Mucopurulent chronic bronchitis
491.20	ICD-9 Dx	Obstructive chronic bronchitis, without exacerbation
491.21	ICD-9 Dx	Obstructive chronic bronchitis, with (acute) exacerbation
491.22	ICD-9 Dx	Obstructive chronic bronchitis with acute bronchitis
491.8	ICD-9 Dx	Other chronic bronchitis
491.9	ICD-9 Dx	Unspecified chronic bronchitis
492	ICD-9 Dx	Emphysema
492.0	ICD-9 Dx	Emphysematous bleb
492.8	ICD-9 Dx	Other emphysema
496	ICD-9 Dx	Chronic airway obstruction, not elsewhere classified
J41	ICD-10 Dx	Simple and mucopurulent chronic bronchitis
J410	ICD-10 Dx	Simple chronic bronchitis
J411	ICD-10 Dx	Mucopurulent chronic bronchitis
J418	ICD-10 Dx	Mixed simple and mucopurulent chronic bronchitis
J42	ICD-10 Dx	Unspecified chronic bronchitis
J43	ICD-10 Dx	Emphysema
J430	ICD-10 Dx	Unilateral pulmonary emphysema [MacLeod's syndrome]
J431	ICD-10 Dx	Panlobular emphysema
J432	ICD-10 Dx	Centrilobular emphysema
J438	ICD-10 Dx	Other emphysema
J439	ICD-10 Dx	Emphysema, unspecified
J44	ICD-10 Dx	Other chronic obstructive pulmonary disease
J440	ICD-10 Dx	Chronic obstructive pulmonary disease with acute lower respiratory infection
J441	ICD-10 Dx	Chronic obstructive pulmonary disease with (acute) exacerbation
J449	ICD-10 Dx	Chronic obstructive pulmonary disease, unspecified
Cystic fibrosis		
277.0	ICD-9 Dx	Cystic fibrosis
277.00	ICD-9 Dx	Cystic fibrosis without mention of meconium ileus
277.01	ICD-9 Dx	Cystic fibrosis with meconium ileus
277.02	ICD-9 Dx	Cystic fibrosis with pulmonary manifestations
277.03	ICD-9 Dx	Cystic fibrosis with gastrointestinal manifestations
277.09	ICD-9 Dx	Cystic fibrosis with other manifestations
E84	ICD-10 Dx	Cystic fibrosis
E84.0	ICD-10 Dx	Cystic fibrosis with pulmonary manifestations
E84.11	ICD-10 Dx	Meconium ileus in cystic fibrosis
E84.19	ICD-10 Dx	Cystic fibrosis with other intestinal manifestations
E84.8	ICD-10 Dx	Cystic fibrosis with other manifestations
E84.9	ICD-10 Dx	Cystic fibrosis, unspecified

Code	Code Type	Description
Acute respiratory failure		
518.51	ICD-9 Dx	Acute respiratory failure following trauma and surgery
518.52	ICD-9 Dx	Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery
518.53	ICD-9 Dx	Acute and chronic respiratory failure following trauma and surgery
518.81	ICD-9 Dx	Acute respiratory failure
518.82	ICD-9 Dx	Other pulmonary insufficiency, not elsewhere classified
518.84	ICD-9 Dx	Acute and chronic respiratory failure
799.1	ICD-9 Dx	Respiratory arrest
J95821	ICD-10 Dx	Acute postprocedural respiratory failure
J95822	ICD-10 Dx	Acute and chronic postprocedural respiratory failure
J9600	ICD-10 Dx	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J9601	ICD-10 Dx	Acute respiratory failure with hypoxia
J9602	ICD-10 Dx	Acute respiratory failure with hypercapnia
J9620	ICD-10 Dx	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia
J9621	ICD-10 Dx	Acute and chronic respiratory failure with hypoxia
J9622	ICD-10 Dx	Acute and chronic respiratory failure with hypercapnia
J9690	ICD-10 Dx	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia
J9691	ICD-10 Dx	Respiratory failure, unspecified with hypoxia
J9692	ICD-10 Dx	Respiratory failure, unspecified with hypercapnia
R092	ICD-10 Dx	Respiratory arrest
Lung cancer		
162.2	ICD-9 Dx	Malignant neoplasm of main bronchus
162.3	ICD-9 Dx	Malignant neoplasm of upper lobe, bronchus or lung
162.4	ICD-9 Dx	Malignant neoplasm of middle lobe, bronchus or lung
162.5	ICD-9 Dx	Malignant neoplasm of lower lobe, bronchus or lung
162.8	ICD-9 Dx	Malignant neoplasm of other parts of bronchus or lung
162.9	ICD-9 Dx	Malignant neoplasm of bronchus and lung, unspecified
C34	ICD-10 Dx	Malignant neoplasm of bronchus and lung
C340	ICD-10 Dx	Malignant neoplasm of main bronchus
C3400	ICD-10 Dx	Malignant neoplasm of unspecified main bronchus
C3401	ICD-10 Dx	Malignant neoplasm of right main bronchus
C3402	ICD-10 Dx	Malignant neoplasm of left main bronchus
C341	ICD-10 Dx	Malignant neoplasm of upper lobe, bronchus or lung
C3410	ICD-10 Dx	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C3411	ICD-10 Dx	Malignant neoplasm of upper lobe, right bronchus or lung
C3412	ICD-10 Dx	Malignant neoplasm of upper lobe, left bronchus or lung
C342	ICD-10 Dx	Malignant neoplasm of middle lobe, bronchus or lung
C343	ICD-10 Dx	Malignant neoplasm of lower lobe, bronchus or lung
C3430	ICD-10 Dx	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C3431	ICD-10 Dx	Malignant neoplasm of lower lobe, right bronchus or lung

Code	Code Type	Description
C3432	ICD-10 Dx	Malignant neoplasm of lower lobe, left bronchus or lung
C348	ICD-10 Dx	Malignant neoplasm of overlapping sites of bronchus and lung
C3480	ICD-10 Dx	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C3481	ICD-10 Dx	Malignant neoplasm of overlapping sites of right bronchus and lung
C3482	ICD-10 Dx	Malignant neoplasm of overlapping sites of left bronchus and lung
C349	ICD-10 Dx	Malignant neoplasm of unspecified part of bronchus or lung
C3490	ICD-10 Dx	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C3491	ICD-10 Dx	Malignant neoplasm of unspecified part of right bronchus or lung
C3492	ICD-10 Dx	Malignant neoplasm of unspecified part of left bronchus or lung

Table E4. Baseline* medication regimen among incident multiple-inhaler triple-therapy (MITT) users immediately preceding MITT initiation.

	MITT users (N=1,831)
Maintenance treatment regimen[†], n (%)	
Maintenance treatment	1,655 (90.4)
No maintenance treatment	176 (9.6)
Medication regimen by class (n=1,655)[‡], n (%)	
LAMA alone	288 (17.4)
Medium-dose ICS/LABA (FDC) alone	237 (14.3)
High-dose ICS/LABA (FDC) alone	188 (11.4)
High-dose ICS/LABA (FDC) + LM	150 (9.1)
Medium-dose ICS/LABA (FDC) + LM	130 (7.9)
LM + LAMA	111 (6.7)
LM alone	108 (6.5)
Low-dose ICS/LABA (FDC) alone	104 (6.3)
Low-dose ICS/LABA (FDC) + LM	55 (3.3)
LAMA/LABA (FDC) alone	27 (1.6)
Medium-dose ICS alone	16 (1.0)
Medium-dose ICS + LM	14 (0.9)
High-dose ICS alone	11 (0.7)
Medium-dose ICS + LAMA	10 (0.6)
High-dose ICS/LABA (FDC) + LM + Anti-IgE	9 (0.5)

Medication classes are categorized into mutually exclusive combinations.

*Baseline period does not include index date for this outcome.

[†]Patients with maintenance medication(s) within the 45 days preceding the index date were classified as having maintenance treatment and those without any maintenance medications within the 45 days preceding the index date were classified as having no maintenance treatment.

[‡]Captured from pharmacy claims only for patients with a maintenance regimen.

FDC; fixed-dose combination; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LM, leukotriene modifier; MITT, multiple-inhaler triple therapy.

Figure E1. Patient identification and attrition

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid.

Figure E2. Maintenance medication classes comprising the index multiple-inhaler triple-therapy (MITT) regimen.

Medication classes are categorized into mutually exclusive combinations.

FDC, fixed-dose combination; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy.

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Commercial and Medicare Part-D
patients with at least 2 diagnosis
codes or asthma in any position on
different dates of service between
01 January 2013 and 31 July 2018
N=1,456,092

Exclusion criteria:
≥1 COPD diagnosis in any position
(01 Jan 2013–31 July 2018)

312,770 patients excluded

Remaining patients
N=1,143,322

Exclusion criteria:
≥1 cystic fibrosis, acute respiratory
failure, or lung cancer
diagnosis in any position
(01 Jan 2013–31 July 2018)

31,705 patients excluded

Remaining patients
N=1,111,617

Exclusion criteria:
At least one pharmacy claim
for an ICS-containing medication
(01 Jan 2013–31 July 2018)

600,672 patients excluded

Remaining patients
N=510,945

Exclusion criteria:
Unknown age, gender, geographic
region, or insurance type

167 patients excluded

Patients with asthma taking
ICS-containing medication
N=510,778

**Additional inclusion criteria for
annual prevalence estimates:**
≥1 asthma diagnosis in any position and
≥1 pharmacy claim for an ICS-containing
medication during the year, age ≥ 18 years
as of the year of the asthma diagnosis,
and continuous enrolment with medical and
pharmacy coverage for the entire year

01 Aug 2017–31 Jul 2018: **N=95,580**
01 Aug 2017–31 Jul 2017: **N=87,820**
01 Aug 2017–31 Jul 2016: **N=75,489**
01 Aug 2017–31 Jul 2015: **N=69,605**

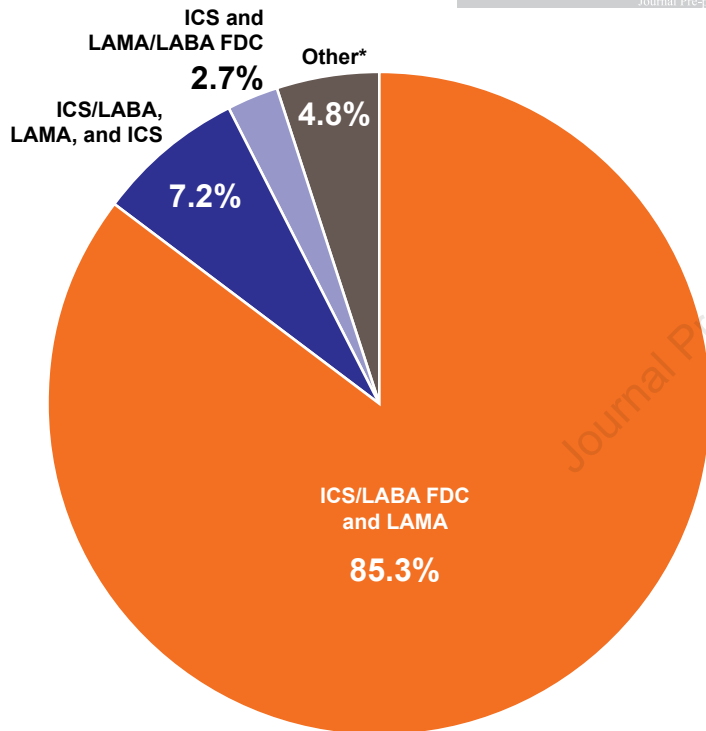
Exclusion criteria:
Unknown age, gender, geographic
region, or insurance type

389 patients excluded

Patients with asthma
N=1,111,228

**Additional inclusion criteria for
annual prevalence estimates:**
≥1 asthma diagnosis in any position during
the year, age ≥ 18 years as of the year of the
asthma diagnosis, and continuous
enrolment with medical and pharmacy
coverage for the entire year

01 Aug 2017–31 Jul 2018: **N=254,069**
01 Aug 2017–31 Jul 2017: **N=238,659**
01 Aug 2017–31 Jul 2016: **N=212,617**
01 Aug 2017–31 Jul 2015: **N=192,350**

***Other Index MITT Components****Total Population
N=1,831**

ICS/LABA and LAMA/LABA	43 (2.4%)
ICS, LABA, and LAMA	30 (1.6%)
ICS, LABA, and LAMA/LABA	5 (0.3%)
ICS/LABA, LABA, and LAMA	4 (0.2%)
ICS, ICS/LABA, LABA, and LAMA	3 (0.2%)
ICS, ICS/LABA, and LAMA/LABA	2 (0.1%)