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SHORT-ACTING BETA-AGONIST UTILIZATION AMONG PATIENTS WITH ASTHMA: A RETROSPECTIVE REVIEW

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ABBREVIATIONS

ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CDL	Contract Drug List
COPD	Chronic obstructive pulmonary disease
DPI	Dry powder inhaler
ED	Emergency department
EIB	Exercise-induced bronchospasm
FDA	United States Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FFS	Fee-for-service
GINA	Global Initiative for Asthma
ICD-10	International Classification of Diseases – 10^{th} revision
ICS	Inhaled corticosteroids
LABA	Long acting $beta_2$ agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MART	Maintenance and reliever therapy
MDI	Metered dose inhaler
NA	Not applicable
NC	Not calculated
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
OCS	Oral corticosteroids
PA	Prior authorization
PDC	Proportion of days covered
PDL	Preferred Drug List
pMDI	Pressurized metered dose inhaler
SABA	Short acting $beta_2$ agonist
SD	Standard deviation
US	United States (of America)

1.0 INTRODUCTION

Asthma is a heterogeneous chronic pulmonary disorder, typically caused by airway inflammation, that is characterized by airway hyperresponsiveness (ie, excessive bronchoconstriction triggered by irritants or allergens), reversible airway obstruction, and recurrent symptoms. Symptoms of asthma are variable and typically include shortness of breath, wheezing, chest tightness, and cough.[1,2] Asthma severity is estimated retrospectively based on the intensity of treatment required to control symptoms.[1] Severe progressive worsening of symptoms (exacerbations) can be life-threatening and unpredictable. People with asthma of all severities and levels of disease control are at risk for exacerbations.[1]

Onset of asthma occurs during childhood for approximately half of cases.[1] Asthma is the most common chronic condition of childhood,[3] affecting an estimated 5.5% of children in Utah in 2021.[4,5] Many adults also have asthma; about 9.7% of surveyed Utahn adults reported having asthma in 2021.[6] Based on United States (US) ambulatory physician visits for asthma that coded asthma severity (34% of all visits) between 2012 and 2015, most patients had mild to moderate asthma. In this dataset, the percentage of visits per asthma severity was as follows: intermittent (11.3%), mild persistent, (10%), moderate persistent (10%), and severe persistent (2.7%).[7] Between 2015 and 2017, an estimated 20% of children and 33% of adults with asthma in Utah were considered to have uncontrolled asthma.[8]

Guideline-recommended treatment options for asthma vary by age and level of asthma control, but regardless of disease severity, guidelines imply that *all patients with asthma should have reliever therapy (ie, rescue therapy for breakthrough symptoms) on hand*.[1,2,9] In other words, those delivered on a scheduled basis may not be required for patients with mild asthma, *but reliever therapy is recommended for all patients with asthma*.[1,9]

Historically, the primary guideline-recommended reliever therapy has been inhaled short-acting $beta_2$ agonists (SABAs), including albuterol or levalbuterol.[2] In 2019, the International Global Initiative for Asthma (GINA) guideline stopped recommending SABA monotherapy for patients with *mild asthma* aged 6 or older, and instead recommended that such patients receive an inhaled corticosteroid (ICS; used as part of an as-needed reliever regimen or on a scheduled basis) with either a SABA or as ICS-formoterol[†] reliever therapy, depending on the patient's age and degree of asthma symptoms.[10] While SABA monotherapy is discouraged by GINA for patients aged 6 and older,[1] SABAs are a potentially life-saving treatment for acute bronchoconstriction and remain a preferred or alternative reliever therapy option in recent guidelines, depending on the patient's age and disease severity.[1,9]

Concerningly, high-frequency SABA use, as monotherapy or in combination with anti-inflammatory treatments (eg, ICS), is a predictor of asthma exacerbations and/or mortality, based on observational studies.[1] Potential harms from an overreliance on SABAs are hypothesized to occur from the lack of anti-inflammatory benefit, and a potentially decreased response to SABAs that develops after regular frequent use.[1] Moreover, using SABAs without ICS (either in the form of as-needed or maintenance therapy) is also associated with poor outcomes.[1] In the US, SABA monotherapy is common, occurring in

[†] Formoterol is a long-acting $beta_2$ agonist (LABA) with a fast onset of effect that is a preferred reliever therapy in combination with ICS for adolescents and adults per GINA; however, in the US, ICS-only and ICS-formoterol inhalers are not FDA-indicated for reliever therapy despite guideline recommendations.

81% of Medicaid-insured patients with mild asthma in one recent study.[11] Adherence to ICS-containing maintenance therapy is also poor (eg, 60% of patients filling maintenance medications ≤ 50% of the time[11]) in patients with mild-to-severe asthma, suggesting many patients are at-risk for underexposure to anti-inflammatory treatments.[1]

Given the concerns with frequent SABA use, this report aims to 1) describe recent international/US guideline recommendations for use of SABAs and maintenance therapies for asthma; and (2) perform a retrospective review of SABA utilization in the Utah Medicaid Fee-for-Service (FFS) asthma population. The retrospective review will describe utilization of SABA inhaler or nebulizer therapies and identify the proportion of patients with frequent SABA use.

2.0 METHODS

Recent (2019-2024) US or global (ie, GINA) guidelines addressing pharmacotherapy for children, adolescents and/or adults with asthma were identified from the following sources (searched January 22, 2024):

- https://www.tripdatabase.com/
  - Searched for keyword 'asthma' and restricted results to target publication years, and guideline publication types
- American Thoracic Society (ATS) guidelines: https://www.thoracic.org/statements/allergy-asthma.php
- Global Initiative for Asthma (GINA) reports: https://ginasthma.org/
- https://www-uptodate-com
  - Reviewed 'society guideline links' on pages for asthma in adolescents and adults, and asthma in children

Background information about asthma, medications for asthma, and frequency of SABA use were collected from focused searches of the following resources:

- Drugs at U.S. Food and Drug Administration (FDA): https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- Dailymed: https://dailymed.nlm.nih.gov/dailymed/
- The drug compendiums Lexicomp (https://online-lexi-com.ezproxy.lib.utah.edu) and Micromedex via DynaMed (https://www.dynamed.com/)
- Centers for Disease Control and Prevention (CDC): CDC.gov
- Recent guidelines from GINA and the National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP)
- Studies cited by GINA and/or NAEPP guidelines or studies cited by those studies, or studies considered similar to guideline-cited studies by pubmed.ncbi.nih.gov/.

2.1 Data Collection and SABA Use Calculations

We performed a descriptive analysis of SABA utilization among Utah Medicaid FFS patients with an asthma diagnosis who lacked other conflicting chronic pulmonary diagnoses (eg, chronic obstructive

pulmonary disease [COPD]) between **October 2022 and September 2023** (the study period). The study period was selected because it was the most recent 12-month period expected to have complete pharmacy and medical FFS claims.

2.1.1 Patient cohort

We identified patients with Utah Medicaid FFS coverage who were diagnosed with asthma and who filled a prescription for an inhaled SABA product during the study period. To eliminate some confounding factors for SABA utilization, we excluded patients with other chronic pulmonary conditions, including COPD and exercise-induced bronchospasm (EIB). Patients were also required to be eligible for Medicaid benefits for at least 2 months out of the 12-month study period; 2 months was considered the minimum duration needed to fill at least 3 SABA inhaler canisters based on Medicaid FFS monthly quantity limits as of February 2024.[12]

Eligible patients were identified using outpatient pharmacy claims for SABA prescription fills (ie, albuterol or levalbuterol inhaler or solution for nebulization) for oral inhalation; inpatient or outpatient claims for an International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes; and months of Utah Medicaid coverage during the study period. The *index date* was defined as the date of the first SABA fill during the study period.

Included patients were Utah Medicaid FFS patients meeting the following criteria during the study period (criteria were applied in the order listed):

1. Have at least 1 outpatient pharmacy claim for an inhaled SABA mono-ingredient product, or combination albuterol sulfate-budesonide (Airsupra) during October 2022 to September 2023.
2. Have at least 1 medical claim for an ICD-10 code for asthma *other than* for EIB *during the 12 months before the index date*.
3. Excluded patients with at least 1 medical claim for an ICD-10 code for a conflicting chronic pulmonary diagnosis (eg, COPD, cystic fibrosis, EIB) between the 12 months preceding the index date and end of observation during the study period.
4. Have Medicaid eligibility for ≥ 2 months during follow-up period (from the index date month to 9/30/2023).

Refer to **Appendix A, Table A1** for details about selecting the patient cohort.

2.1.2 SABA Use

For each included patient, we added up the quantity of inhaled SABA products filled during the study period. Total SABA quantities filled were normalized to a number of 200-actuation canister equivalents in order to standardize across different inhaled dosage forms. The quantity of SABA inhaler or nebulizer vials filled was determined for each unique pharmacy claim using product-specific rules based on the dispensed drug quantity and package size; the quantity filled was then converted to 200-actuation canister equivalents (see **Appendix A, Table A2**). To convert SABA nebulizer products to 200-actuation canister equivalents, we assumed that 100 single-dose vials is approximately equivalent to one 200-actuation SABA inhaler canister based on the recommended dose from the NAEPP guideline and/or prescribing information.[2,13-15]

Frequent SABA use was defined as filling (as outpatient pharmacy fills) ≥ 3 SABA 200-actuation canister equivalents (ie, SABA inhaler and/or nebulizer vials) within the 12-month study period. This definition is derived from the threshold that GINA advises is associated with an increased risk of exacerbations, based on observational evidence.[1]

2.1.3 Maintenance Therapy Definition

"Maintenance"[‡] therapy medications are GINA-recommended preferred or alternative therapies from the 2023 guideline that can be used as monotherapy for one or more treatment stages, including inhaled corticosteroid (ICS)-based therapies or leukotriene receptor antagonists (LTRAs) such as montelukast.[1] ICS-based therapies include ICS monotherapy inhaler or nebulizer products, and ICS-combination products (eg, ICS with long-acting beta$_2$-agonists [LABAs], referred to as ICS-LABA). We did not consider products not recommended as monotherapy for asthma maintenance treatment (eg, LABA-only products, monoclonal antibodies), since our goal was to identify patients filling a prescription for a single product that could satisfy a complete guideline-line recommended maintenance or ICS-containing regimen. Refer to **Appendix A, Table A3** for information about how we identified and defined maintenance therapies using outpatient pharmacy claims data.

2.1.4 Descriptive Analysis

We used descriptive statistics to characterize SABA utilization during the study period in our overall cohort and by subgroups; subgroup categories were defined by observation interval (total months of Medicaid eligibility in the study period following each patient's first SABA fill), patient age as of the index date, and maintenance therapy proportion of days covered (PDC) during the observation interval. For both the overall cohort and these subgroups, we calculated the mean, standard deviation (SD), median, and range (25th to 75th percentile) for the total SABA canister equivalents filled. To further describe SABA utilization, we also determined the proportions of each cohort or subgroup with total canister equivalents filled for the following categories: <3, 3, 4-6, 7-9, 10-11, and ≥ 12 canister equivalents. Because patients could have different durations of observation, we also calculated the mean SABA canister equivalents filled per month of Medicaid eligibility (the sum of all SABA canister equivalents filled divided by the sum of the number of observation interval months).

Observation interval ranges (ie, duration of Medicaid eligibility in months after the first SABA fill during the study period) are designated as 2-3, 4-6, 7-9, and 10-12 months. Subgroup categories for patient age were selected based on commonly defined age ranges for different treatment recommendations in GINA and NAEPP guidelines (ie, 0-5, 6-11, and ≥ 12 years of age), with the age of the patient defined as their age at the time of the first indexed SABA fill (ie, index date).

For the maintenance therapy[‡] subgroup (ie, the subset of patients who filled a prescription for a medication sufficient to fulfill a GINA-recommended maintenance therapy [ie, ICS-containing or LTRA product] and/or GINA-recommended as-needed ICS therapy), we calculated the PDC by at least 1 maintenance therapy over the total observation interval for each patient using the days' supply and fill

[‡] We refer to the medications as "maintenance" therapies for simplicity, although some patients could have been using ICS therapies as-needed as part of a guideline-recommended reliever regimen (ie, ICS-formoterol, ICS-SABA, or ICS as a single-ingredient product for use whenever a SABA is used).

date from outpatient pharmacy claims for each maintenance therapy prescription during the study period. Prescription fills for a LTRA and/or ICS-containing medication counted toward the days covered with a maintenance medication; however, if the days' supply for a patient's LTRA and ICS-containing prescription overlapped, each overlapping day with both types of medications counted as only one covered day. Otherwise, PDC was calculated carrying forward any overlapping supply of medication from the same class (LTRA or ICS-containing therapy) between successive fills during periods with Medicaid eligibility. Maintenance therapy intensity expressed as PDC was provided as the following ranges: ≥75%, 25%-<75%, >0%-<25%, and 0% (ie, 0% meaning no fills for maintenance/as-needed ICS medications). PDC is an accepted measure of medication adherence,[16,17] with PDC proportions of approximately 75% or higher associated with a reduced risk of asthma exacerbations.[17] Refer to **Appendix A, Table A3** for PDC calculation details.

3.0 DEFINITION OF AND CONCERNS WITH FREQUENT SABA USE PER OBSERVATIONAL STUDIES, GUIDELINES, AND EXPERT GUIDANCE

Observational studies, recent US/international guidelines and expert guidance generally agree that filling prescriptions for ≥ 3 SABA canisters per year is associated with worse asthma outcomes, and that the magnitude of associated risks increases with greater SABA usage.[1,2,11,18]

3.1 Prevalence and Outcomes of Frequent SABA Use from Select Observational Studies

Frequent use of SABAs, including as SABA monotherapy or in combination with maintenance therapy, is associated with increased risk for exacerbations and/or mortality.[1] The following summarizes information from select observational studies about frequent SABA use:

- Many asthma patients fill ≥ 3 canisters per year: among over 1,000,000 patients from the US and other countries, about 40% of adults and adolescents were prescribed/filled prescriptions for ≥3 SABA canisters per year.[11]
- Generally, frequent SABA usage (≥3 canisters/year compared to ≤2 canisters/year) is associated with an increased risk of asthma exacerbations (eg, oral corticosteroid use, or emergency department [ED] or hospitalization for asthma),[11,18] and increased mortality[18] regardless of treatment with ICS and asthma severity. In a study from Sweden, the association with increased exacerbations and mortality was dose-related, with incremental increases in the observed hazard of exacerbation or death per SABA canister usage category increase from ≥3 up to ≥11.[18]
- Past 90-day frequent use of nebulized SABAs may carry a greater risk of poor outcomes (ie, ED visits or hospitalizations for asthma) than frequent SABA inhaler use. In a single study, past 90-day SABA nebulizer use, but not SABA inhaler use, was associated with poor asthma outcomes.[19]
- Compared with adults and adolescents (≥12 years old), less evidence about risks of frequent SABA use in children is available. Among Medicaid-covered children (4-17 years old), use of ≥3 SABA canisters per year carried a nearly 2-fold increased risk of exacerbations compared to using ≤2/year.[20] Frequent SABA use (≥3 canisters) per year was associated with an increased risk of exacerbation among Swedish children ages 6-11 years after controlling for treatment step.[21]

3.2 Recent Guideline Definitions of Frequent SABA Use

Both the NAEPP (2007/2020) and GINA (2023) guidelines address frequency of SABA use with primarily non-graded recommendations for monitoring asthma symptom control. In addition, both guidelines provide background information about the relationship between frequent SABA use and asthma exacerbations. Refer to **Table 1** for information about frequent SABA use extracted from these guidelines.

Regarding the frequency of using SABAs to relieve symptoms, GINA advises that past-month use of a SABA-only reliever therapy ≥ 2 times per week (for ages ≥ 6 years) or ≥ 1 time per week (for age <6 years) is one symptom of poor asthma control.[1] Regardless of age, the NAEPP advises that using a SABA ≥ 3 times per week is a potential sign of uncontrolled asthma symptoms. Increasing SABA use regardless of the frequency is also a sign of poor symptom control.[9] Importantly, using SABAs prophylactically to prevent EIB should not count toward the number of SABA uses, according to both guidelines.[1,2,9]

GINA points to using ≥ 3 SABA canisters per year (200-actuation/inhaler) as a risk factor for asthma exacerbations.[1] Risks from frequent SABA usage may increase incrementally beyond the threshold of using 3 or more canisters per year. The NAEPP (2007) advises that using ≥ 1 canister every 1-2 months (ie, 6-12 canisters/year) is associated with an increased risk of severe exacerbations,[2] while GINA describes that each incremental step up in annual SABA canister usage, from 3-5 to 6-10 and ≥ 11, is associated with increased mortality compared with using ≤ 2 canisters per year, regardless of asthma severity.[1,18]

Notably, while guidelines highlight concerns with higher frequency SABA use, at no point do they advise or imply cutting off patient's access to reliever therapy after a particular threshold of use. Rather than deny access to reliever therapy, options implied include switching the reliever therapy (eg, SABA to ICS-formoterol for potential appropriate cases), adding or increasing the intensity of maintenance therapy if an option for the patient, and optimizing adherence and administration technique of therapies.

3.2.1 Recent Expert Guidance about Frequent SABA Use

Lugogo et al (2023) used a modified Delphi process to develop expert opinion recommendations about the SABA usage threshold associated with an increased risk of exacerbations, and how clinicians should monitor and react to frequent SABA use. Informed by an evidence review, experts agreed that using ≥ 3 SABA canisters annually carries increased risks for exacerbations and mortality. **Providers should monitor patient's SABA usage (eg, by patient report, monitoring refills, or digital tools), but should also ensure patients have access to SABA refills**. When addressing frequent SABA use, experts generally agreed that clinical action "…should not depend on a specific threshold but rather an increase from the patient's baseline use" (page 627). For example, most experts agreed that a 50-100% increase in SABA usage above the patient's baseline requires intervention. Multiple interventions for high/increased SABA usage were considered options, including but not limited to, reviewing inhaler technique, eliciting more information to stratify risk (eg, symptom severity, exacerbation history), providing asthma education, and changing medications.[22]

Table 1. Guidance from Recent US and International Guidelines about Frequency of SABA Use

Applicable population(s)	Definition of high frequency SABA use or related information
Global Initiative for Asthma (GINA), 2023[1]	
Adults, adolescents, and children 6-11 years	• An asthma exacerbation risk factor, as one indicator of uncontrolled symptoms: ○ Use of ≥ 3 canisters (200-dose) per year ▪ Use of ≥ 1 canister per month carries highest risk • Use of a SABA-only reliever **≥ 2 times per week** (over the past month)[a] is 1 of 4 screening symptoms for asthma control ○ Uncontrolled = presence of ≥ 3 symptoms
Children ≤ 5 years	• Use of a SABA-only reliever **≥ 1 time per week** (over the past month)[a] is 1 of 4 screening symptoms for asthma control ○ Uncontrolled = presence of ≥ 3 symptoms
Not specified	• Frequent SABA use, particularly use of ≥ 1 SABA canister/month, is associated with an increased risk of asthma-related death
National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), 2020 Focused Update[9]	
Adults, adolescents, children 0-11 years	• SABA use >2 times per week[a] = one indicator of poor asthma control
National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), 2007 Report (precursor to and part of the 2020 update)[9]	
Not specified	• Daily chronic scheduled use of SABA is not recommended (A[b]) ○ Risks are likely greatest when used as a SABA-only regimen without concomitant ICS • Use of >1 SABA canister every 1-2 months is associated with increased risk (or is a predictor) of exacerbations and poor outcomes • >1 SABA canister (200-dose) in 1 month[a] = likely poor asthma control

Abbreviations: ICS, inhaled corticosteroids; SABA, short-acting beta$_2$-agonist

[a] When SABA is used to treat symptoms; excludes SABA use before exercise to prevent exercise-induced bronchospasm.

[b] A-level evidence from robust randomized controlled trials.

4.0 SELECT RECENT US OR INTERNATIONAL GUIDELINE RECOMMENDATIONS AND SABA FDA INDICATIONS

We reviewed 2 recent asthma clinical practice guidelines commonly used in the US for recommendations about reliever and maintenance therapies. Reviewed guidelines include the GINA guideline, updated in July 2023,[1] and the NAEPP guideline, which originated in 2007[2] and was followed by a focused update completed in 2020.[9] The NAEPP focused update selectively addressed 6 topics so both the 2007 guideline and 2020 update were referenced for recommendations, with an emphasis on the 2020 update.

In both guidelines, asthma treatment is addressed in "steps." Treatment steps roughly correspond with the patient's asthma severity, typically ranging from mild (steps 1-2), to moderate (steps 3-4), and severe (steps 5-6).[1,2,9] Selection of the appropriate treatment step is guided by the patient's age, severity of presenting symptoms, risk factors for poor outcomes, and response to treatment (ie, asthma control). The NAEPP also describes asthma as intermittent (step 1) or persistent (steps 2 and above).[2,9] It is important to recognize that asthma severity corresponds to the treatment level *needed to control symptoms*, and exacerbations or severe symptoms can occur at any disease severity.[1] Pharmacologic regimens for asthma can include maintenance therapy, which is administered on a scheduled basis, and reliever therapy taken as needed to manage breakthrough acute asthma symptoms.[1] **Notably, reliever medication is indicated at all steps**.

Reviewed guidelines recommend reliever and maintenance therapies as preferred, alternative, or other recommended options. Generally, preferred options are those with superior efficacy and/or safety evidence with robust high-quality evidence to support use.[1,2,9] While GINA recommends using shared decision-making to select a patient-specific option at the individual level, preferred therapies are the treatment(s) of choice at the population level.[1] According to the NAEPP, alternative options are less effective or have lower-quality supportive evidence compared with preferred options; alternative options may be selected based on patient preference, cost, or when patients are well-controlled on an alternative regimen.[9] Because GINA created a preferred and alternative treatment "track" for the oldest age group (age 12+), alternative options are also sometimes called "other" options.[1]

While intermittent ICS (eg, as-needed ICS-formoterol as reliever therapy) use is addressed by the 2020 NAEPP update, the update did not consider some populations/comparisons because they were not part of the pre-planned guideline questions. Key populations for as-needed ICS-formoterol <u>not addressed</u> by the NAEPP update include intermittent asthma (treatment step 1) or severe asthma (treatment step 5+) for the comparison of ICS-formoterol to SABA, both given as-needed; and maintenance low-dose ICS with as-needed SABA compared to as-needed ICS-formoterol for people with mild persistent asthma (treatment step 2).[2] This should be considered when interpreting the NAEPP's recommendations for who should receive as-needed ICS-formoterol.

The following sections address relevant background information from guidelines about SABA use (eg, is there a preferred SABA, and when is SABA therapy recommended) and maintenance medications, with a focus on addressing at what treatment step maintenance medications are recommended.

4.1 SABA Options and Recommended Delivery Devices by Age

All patients with asthma are at risk of exacerbations, thus reliever medications are indicated for all patients to be able to respond to breakthrough asthma symptoms or exacerbations (versus solely rely on emergency/hospital services). Because symptoms are unpredictable (perhaps apart from EIB), patients should always have a reliever medication on hand. Guidelines recommend a reliever therapy for all patients with asthma, regardless of their treatment step.[1,9] Reliever treatment options include inhaled SABAs, as monotherapy or combined with an ICS, and inhaled ICS-formoterol (an ICS-LABA combination inhaler). **Table 2** summarizes the type of reliever therapy recommended for as-needed use by recent US and international guidelines.

Depending on age and treatment step, ICS-formoterol is recommended as either as-needed reliever therapy only, or as a one-inhaler option for both scheduled maintenance and as-needed reliever therapy called MART (maintenance and reliever therapy).[1,9] ICS-formoterol is the *preferred reliever option* for(a) all adults and adolescents aged ≥ 12 years, regardless of treatment step (per GINA),[1] (b) **only** adults and adolescents requiring stage 3-4 treatment (per NAEPP),[9] and (c) children aged 5 (NAEPP), or 6 to 11 years requiring stage 3-4 treatment (per GINA; as an equal preference to SABAs).[1,9]

Inhaled SABA reliever therapy is an *alternative option* for adults and adolescents aged ≥ 12 years (according to both guidelines) and children aged 5-11 years and older in steps 3-4 (per NAEPP), and the *preferred option* for all children aged 0-4 years (according to both guidelines), children aged 5 years (per GINA), and children aged 6-11 years in steps 1, 2, or 5 (according to both guidelines).[1,9] For children 6-11 years old in steps 3-4, GINA considers ICS-formoterol (as MART) and as-needed SABA to be *equally preferred* options.[1] Because GINA recommends that each patient receive ICS in their overall regimen (ie, as intermittent use with reliever therapy, or as scheduled maintenance therapy), GINA prefers using an ICS inhaler whenever a SABA inhaler is used (ie, ICS-SABA as 2 separate products or combination inhaler product) to SABA monotherapy for children ages 6-11 years at treatment step 1; ICS-SABA (not SABA-only) is also the alternative reliever option to ICS-formoterol for adults and adolescents at step 1.[1] At step 2 for children 6-11, GINA prefers SABA reliever to ICS-SABA because it is preferred that such patients receive scheduled maintenance ICS (with as-needed SABA).[1] ICS-SABA is an alternative option for adults and adolescents 12 years or older at step 2 (per the NAEPP)[9] or steps 2-5 (per GINA).[1]

Where SABA is indicated for as-needed symptom relief, neither GINA (2023) nor the NAEPP (2007/2020) formally prefer a particular type of inhaled SABA over another (ie, albuterol vs. levalbuterol).[1,2,9] The minimum US Food and Drug Administration (FDA)-approved age for inhaled albuterol and levalbuterol products varies with respect to asthma treatment:

- Levalbuterol hydrochloride concentrate nebulizer solution for inhalation is indicated for children and adults aged 6 years or older.[14] Levalbuterol tartrate inhalation aerosol (Xopenex HFA) is indicated for adults and children aged 4 years or older.[15]
- Indications for albuterol vary by product type and dosage. Generally, albuterol sulfate metered dose inhalers (MDIs)/pressurized metered dose inhalers (pMDIs) or dry power inhalers (DPIs) are indicated for people 4 years of age or older, while the nebulizer solutions are indicated for people aged 2 or older.[13,23]

- The only combination ICS-SABA product as of February 2024, albuterol-budesonide (Airsupra) is FDA-indicated for as-needed treatment for of bronchoconstriction, and for reducing asthma exacerbations among adults aged 18 years or older (but not as maintenance therapy).[24] Albuterol-budesonide is not indicated as MART or regular maintenance therapy,[24] and it can be used with ICS or ICS-LABA maintenance therapy.[1,25]

Regarding the type of delivery device (inhaler or nebulizer), both GINA (2023) and NAEPP (2007) generally prefer using an inhaler regardless of age, *provided the patient or caregiver can successfully use the device*.[1,2] In non-acute settings, inhalers (MDI or DPI) are similarly effective to nebulizers, while nebulizers carry a higher risk of spreading infections and are considered less cost-effective.[1] Usually, nebulizers are limited to patients unable to effectively use a MDI in combination with a spacer or valved holding chamber (VHC), or spacer/VHC and facemask.[1,2] GINA encourages using a shared decision-making approach to selecting the delivery device.[1] Refer to **Table 2** for details about the recommended delivery device by age.

4.2 Role of SABAs in Treatment of Exacerbations per GINA (2023)

In addition to providing quick relief of breakthrough asthma symptoms, SABAs have an important role in managing asthma exacerbations. An asthma exacerbation (ie, flare up) is a state of worsened asthma symptoms to a magnitude that requires additional treatments/treatment changes. Exacerbations are usually triggered by an external factor such as environmental exposures (eg, allergens or poor air quality) or viral respiratory infections and can occur suddenly without warning and/or without an identified trigger.[1]

Depending on exacerbation severity and provider's written instructions to patients (ie, asthma action plans), asthma exacerbations can be treated at home. Self-managed treatment of an exacerbation typically includes increased use of the patient's designated reliever (ie, ICS-formoterol, SABA, or ICS-SABA); and for children and adults ≥ 6 years old, increased use of maintenance therapy (or initiating ICS therapy), and possibly, initiation of oral corticosteroids (OCSs) for severe exacerbations[§]. SABAs are a guideline-recommended reliever option for management of an exacerbation at home (ie, in the ambulatory setting); and the usual reliever therapy for treatment of asthma in healthcare settings per GINA.[1]

See **Appendix B** for details about the definition of an asthma exacerbation, and an overview of the treatment approach of an exacerbation managed in the inpatient/emergency setting according to GINA (2023).

[§] We infer that this summary of GINA's guidance on self-management of asthma exacerbations is intended for both children 6-11 years old and adolescents and adults; however, it is likely, but not clear whether the guidance is intended for 6–11-year-old patients.

Table 2. Recommended SABA Reliever Options[a] by Age and Treatment Step and Preferred SABA Type and/or Administration Route in Recent US/International Guidelines

Population	Treatment Step	Global Initiative for Asthma (GINA), 2023[1]	
		Is an inhaled SABA reliever (as-needed) an option[b]?	**SABA Options and/or Administration Route, if specified**
Adults and Adolescents (aged 12 or older)	1	Yes, as ICS-SABA[c] (alternative option). As-needed ICS (LD)-formoterol is the *preferred reliever.*	• Any inhaled SABA can be used (eg, albuterol or levalbuterol) • Inhalers (with a spacer and face mask if needed) are suggested over nebulizers, as long as the patient can use the inhaler successfully • Individualize selection of an inhaler using a shared decision-making approach[d] ○ DPIs may be difficult for some elderly patients to use ○ When an inhaler is prescribed, try to prescribe the same types of inhalers (ie, avoid prescribing a pMDI and DPI to the same person)
	2	Yes, as ICS-SABA[c] or SABA (alternative options) **As-needed** ICS (LD)-formoterol is the *preferred* reliever, *for all steps* including **as MART for steps 3-5**	
	3		
	4		
	5		
Children (aged 6-11 years)	1	Yes, as ICS-SABA[c] (preferred) or SABA (alternative option)	
	2	Yes, SABA (preferred) or as ICS-SABA[c] (alternative option)	
	3–4	Yes, as SABA. As-needed ICS-formoterol is also an option as MART.	
	5	Yes, as SABA	
Children (aged 5 years or younger)	1	Yes, as SABA	• Any inhaled SABA can be used • Recommended delivery device(s) vary by age: ○ <u>Age 0-3 years</u> ▪ Preferred: pMDI + spacer + face mask ▪ Alternative: nebulizer + face mask (suggested only if a spacer cannot be successfully used) ○ <u>Age 4-5</u> ▪ Preferred: pMDI + spacer + mouthpiece ▪ Alternative: pMDI + spacer + face mask, or nebulizer + mouthpiece or face mask ○ DPIs may not be suitable for children ≤ 5 years old
	2		
	3		
	4		

Population	Treatment Step	National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), 2020 Focused Update[9c] and/or 2007 Report[2]	
		Is a SABA reliever (as-needed) an option[b,c]?[9]	**SABA Options and/or Administration Route, if specified**
Adults and Adolescents (aged 12 or older)	1	Yes, as SABA	• Any inhaled SABA can be used (eg, albuterol or levalbuterol)(2007/2020)[2,9] • Typical target ages for aerosol delivery devices (per 2007 guideline)[2]: ○ MDI (age ≥ 5 years) ○ DPI (age ≥ 4 years) ○ Nebulizer is an option for "Patients of any age who cannot use MDI with VHC and face mask" (page 251)[2] • Typical target ages for delivery devices (per 2007 guideline)[2]: ○ Spacer or VHC (age ≥ 4 years) ○ VHC with a face mask (age <4 years)
	2	Yes, as SABA or ICS-SABA[c]	
	3	Yes, as SABA (alternative option) **As-needed** ICS-formoterol is the *preferred reliever*, **as MART**	
	4		
	5	Yes, as SABA	
	6		
Children (aged 5-11 years)	1	Yes, as SABA	
	2		
	3	Yes, as SABA (alternative option) **As-needed** ICS-formoterol is the *preferred reliever*, **as MART**	
	4		
	5	Yes, as SABA	
	6		
Children (aged 0-4 years)	1–6	Yes, as SABA	

Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LD, low dose; MART, maintenance and reliever therapy; MDI, metered dose inhaler; pMDI, pressurized metered-dose inhalers; SABA, short-acting beta$_2$-agonist; VHC, valved holding chamber

[a] *Includes guideline recommendations for regular as-needed use of relievers. Special considerations for using SABAs during an exacerbation requiring treatment in healthcare settings are not addressed.*

[b] ***Appropriateness of the reliever therapy depends on the maintenance therapy used, as applicable. Refer to the respective guidelines for details.***

[c] *ICS use directly following any SABA use (as multiple inhalers) or administered together as a combination-inhaler (eg, albuterol-budesonide [Airsupra]).*

[d] *Applies to all patients, including for children ages 0-5 years. GINA makes the most specific recommendations about the type of device for children 0-5 years, so these recommendations are presented separately from the other age groups.*

4.3 Asthma Control Assessment

Frequency of SABA usage is only one aspect of assessing a patient's asthma control and the need to make changes to a patient's asthma regimen. The following is an overview of some factors to consider when assessing asthma control, but it should not be considered exhaustive.

Controlling asthma symptoms is an asthma treatment goal. Both GINA (2023) and the NAEPP (2007) guidelines define asthma control as the extent to which observable asthma symptoms persist after treatment, or the degree of symptomatic improvement achieved with treatment. Asthma control is typically assessed in two domains: frequency and severity of recent symptoms (ie, impairment) and risk factors for poor outcomes (ie, risks).[1,2] One option for assessing impairment is using a standardized questionnaire; examples of questionnaires with accepted validity are the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ).[1,9]

GINA and NAEPP (2007) recommend assessing similar symptoms for the impairment domain of asthma control.[1,2] Whereas lung function (eg, by forced expiratory volume in 1 second [FEV_1]) is recommended as a domain to monitor for impairment by NAEPP,[2] GINA recommends its use as part of monitoring risks.[1] Since GINA provides more recommendations, we focused on their specific recommendations for assessment of asthma control. Below are examples of other factors indicating the level of control for patients with asthma aged ≥ 6 years per the GINA (2023)[1]:

- In addition to SABA use ≥ 2 times/week (excluding to prevent EIB), providers should assess for past month evidence of asthma symptoms: (a) frequent (≥2 times/week) daytime symptoms, (b) symptoms at night causing awakening, and (c) activity limitations resulting from asthma.
    - Good symptom control is the absence of any of these symptoms, while partial- and un-controlled are considered evidence of 1-2 or 3-4 symptoms, respectively.
- Evidence of risk factors for poor outcomes:
    - There are many potential risk factors, falling into the domains of uncontrolled asthma symptoms (eg, past-year severe exacerbation, frequent SABA use, certain comorbidities), development of persistent airflow restriction (eg, low FEV_1, tobacco smoke exposure), and medication side effects (eg, incorrect use of inhalers, high corticosteroid requirement).

Impairment and risks should also be assessed for children aged 5 years or younger. GINA recommends assessing similar factors to those recommended for older children and adults.[1]

Asthma control along with treatment adherence, proper inhaler usage, comorbidities, and environmental factors should be considered for treatment changes (eg, to step-up treatment).[1,9] For certain potentially modifiable risks, GINA makes specific treatment strategy recommendations for adults and adolescents (see recommendations on page 85 of GINA 2023).[1] Overall, treatment should be individualized, considering the patient's asthma control level and risks factors, unique characteristics, treatment preferences, and goals.[1]

4.4 Maintenance Therapy Options

Asthma maintenance therapies are those treatments used on a continuous and scheduled basis (eg, daily use). Most maintenance therapies target airway inflammation to improve asthma symptoms and reduce the risk of exacerbations.[1] Examples of guideline-recommended maintenance therapies are ICSs, used with or without LABAs, long-acting muscarinic antagonists (LAMAs), oral LTRAs and/or injectable biologic therapies. Oral LTRAs are also an option for stand-alone maintenance therapy without ICS.[1,2,9]

Table 3 provides an overview of preferred or alternative maintenance therapy options according to GINA (2023) and NAEPP (2007/2020). For GINA, Table 3 shows maintenance therapies recommended for ongoing treatment. Initial treatment options per GINA vary slightly from those suggested for ongoing treatment; initial treatment intensity should be selected based on the patient's presenting symptoms.[1] Both guidelines recommend selecting maintenance therapy based on the patient's age and needs for asthma control.[1,9]

GINA and the NAEPP recommend maintaining the lowest treatment step which successfully achieves symptom control and prevention of exacerbations.[1,9] Depending on symptom control and risk factors for exacerbations, maintenance therapy can be intensified (ie, stepped up a level) or reduced (ie, stepped down a level). Before stepping up treatment, it is recommended to ensure modifiable risk factors are well-managed (eg, ensure appropriate inhaler technique, remove persistent exposures to allergens/irritants if possible), ensure asthma is the correct diagnosis, and assess management of comorbidities that could be impacting respiratory symptoms.[1,9]

Maintenance therapy is recommended for people with moderate or severe asthma by GINA and the NAEPP, and depending on age, it is recommended or is an option for mild persistent asthma (ie, **step 2**).[1,9] When maintenance therapy is recommended, ICS-containing therapy is the preferred or alternative option for most ages and treatment steps, with other therapies added to ICS to intensify treatment.[1,9] Using the same inhaler as both maintenance and reliever therapy (MART) is a preferred option at for patients aged ≥ 5 years old treatment steps 3 and 4 (NAEPP); or for patients ≥ 12 years old at steps 3-5 (GINA); or MART with ICS-formoterol is an option (equally preferred to ICS with as-needed SABA) at steps 3-4 for ages 6-11 (GINA).[1,9] LTRA monotherapy is an alternative/other option at step 2 therapy for all ages[1,9]; ICS-containing therapy is preferred because LTRA is less effective than regular ICS (A-level evidence, according to GINA).[1] Although the older NAEPP guideline (2007) considers theophylline, cromolyn, nedocromil and zileuton as alternative maintenance options for some patients,[2] these agents are not among recommended maintenance options by GINA (2023) due to efficacy or safety concerns.[1]

GINA recommends that patients ≥ 6 years old with mild asthma receive ICS-containing therapy. As-needed SABA monotherapy (without as-needed ICS or scheduled ICS) **is an option for all ages at treatment step 1 per the NAEPP[9] whereas GINA only considers SABA monotherapy to be a step 1 option for ages 0-5 years old**.[1] **GINA's rationale for eliminating SABA monotherapy at step 1 for age ≥ 6 years is that people with mild intermittent asthma are at risk for fatal exacerbations and have been shown to respond to ICS therapy**. In other words, **while SABAs are an option for reliever therapy in all patients**, **GINA recommends that they be used along with ICS therapy** (either intermittently or scheduled, depending on the age/step) for most scenarios. The recommendation that all patients start an ICS-containing medication also emphasizes the importance from the outset, and helps patients recognize the importance of ICS-containing medication, possibly preventing over-reliance on SABAs.[1]

Table 3. Preferred and Alternative Medication Option(s)[a,b] for Recommended Maintenance Therapy in Recent US Guidelines, by Age and Treatment Step

Population	Treatment Step	Global Initiative for Asthma (GINA), 2023[1]	
		Preferred or Alternative Option[c]	Other Option(s) with Less Evidence or Fewer Indications[c]
Adults and Adolescents (aged 12 or older)	1	No maintenance therapy	No other option
	2	No maintenance therapy or ICS (LD)	LTRA
	3	ICS (LD)-formoterol (as MART) or ICS (LD)-LABA	ICS (MD), or +LTRA
	4	ICS (MD)-formoterol (as MART with as-needed ICS[LD]), or ICS (MD or HD)-LABA	+LAMA, or +LTRA, or switch to ICS (HD)
	5	+LAMA and/or switch to ICS(HD)-formoterol or ICS(HD)-LABA and/or +biologic therapy	+Azithromycin (adults only) or +LTRA or, as last-line, OCS (LD)
Children (aged 6-11 years)	1	No maintenance therapy	ICS (LD)
	2	ICS (LD)	LTRA
	3	ICS (LD)-LABA, or ICS (MD), or ICS (VLD)-formoterol (as MART)	ICS (LD) + LTRA
	4	ICS (MD)-LABA, or ICS (LD)-formoterol (as MART)	+tiotropium or +LRTA
	5	Switch to ICS (HD)-LABA, or +biologic therapy	As last-line, +OCS (LD)
Children (aged 5 years or younger)	1	Insufficient evidence for scheduled maintenance therapy	Brief ICS during viral illness
	2	ICS (LD)	LTRA, or brief ICS during viral illness
	3	ICS (double-LD)	ICS (LD) + LTRA
	4	ICS (double-LD)	+LTRA, or more frequent ICS, or +intermittent ICS or +LABA or +brief OCS (LD)

Population	Treatment Step	National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), 2020 Focused Update[9,d]	
		Preferred Option[c]	Alternative Option[c]
Adults and Adolescents (aged 12 or older)	1	No maintenance therapy	No alternative
	2	No maintenance therapy, or ICS (LD)	LTRA, or cromolyn, or nedocromil, or theophylline
	3	ICS (LD)-formoterol (as MART)	ICS (MD), or ICS (LD)-LABA, or ICS (LD)+LAMA, or ICS (LD)+LTRA, or ICS (LD)+ theophylline or zileuton
	4	ICS (MD)-formoterol (as MART)	ICS (MD)-LABA, or ICS(MD)-LAMA, or ICS(MD)+LTRA, or ICS(MD)+theophylline or zileuton
	5	ICS (MD or HD)-LABA+LAMA ± biologic therapy[e]	ICS (MD/HD)-LABA, or ICS (HD)+LTRA, ± biologic therapy[e]
	6	ICS (HD)-LABA + OCS ± biologic therapy[e]	No alternative

Abbreviations: +, add this to another therapy; ±, with or without this additional therapy; HD, high dose; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic agonist; LD, low dose; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; MD, medium dose; OCS, oral corticosteroid; SABA, short-acting beta$_2$-agonist; VLD, very low dose;

[a] This is intended as a brief overview of maintenance options for ongoing (not necessarily initial) regularly scheduled treatment; please refer to the respective guidelines for details.

[b] All patients should receive a reliever therapy regardless of whether they receive maintenance therapy. See Table 2 for reliever therapy recommendations.

[c] Although not always specified by guidelines, generally, maintenance therapies are to be administered every day (or multiple times per day) except for some biologic therapies. Refer to guidelines for additional details and dosing guidance by product type and age group and to section 5.1 of this report regarding intermittent ICS treatment

[d] The 2020 report is a targeted update to the original 2007 guideline. Recommended maintenance therapies in this table include those with evidence updated for the 2020 guideline (eg, ICS options), along with other therapies recommended in 2007 that were not considered for an evidence update; therefore, some treatments considered as options by the guideline may no longer be in favor based on recent evidence.

[e] Biologic therapy is neither a preferred or alternative option in the NAEPP 2020 guideline; it is an adjunctive option to be considered at treatment step 5 or step 6

Table 3. Preferred and Alternative Medication Option(s)[a,b] for Recommended Maintenance Therapy in Recent US Guidelines, by Age and Treatment Step

Population	Treatment Step	National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), 2020 Focused Update[9,d]	
		Preferred Option[c]	Alternative Option[c]
Children (aged 5-11 years)	1	No maintenance therapy	No alternative
	2	ICS (LD)	LTRA, or cromolyn, or nedocromil, or zileuton, or theophylline
	3	ICS (LD)-formoterol (as MART)	ICS (MD) or ICS (LD)-LABA, or ICS (LD)+LTRA, or ICS (LD)+theophylline
	4	ICS (MD)-formoterol (as MART)	ICS (MD)-LABA, or ICS (MD)+LTRA, or ICS (MD)+theophylline
	5	ICS (HD)-LABA ± omalizumab	ICS (HD)+LTRA, or ICS (HD)+theophylline, ± omalizumab
	6	ICS (HD)-LABA + OCS ± omalizumab	ICS (HD)+LTRA+OCS, or ICS(HD)+theophylline +OCS, ± omalizumab
Children (aged 0-4 years)	1	Brief ICS during respiratory viral illness	No alternative
	2	ICS (LD)	Montelukast, or cromolyn
	3	ICS (MD), or for age 4+, may follow step 3 treatment for ages 5-11	No alternative
	4	ICS (MD)-LABA, or for age 4+, may follow step 4 treatment for ages 5-11	ICS (MD) +montelukast, or for age 4+, may follow step 4 treatment for ages 5-11
	5	ICS (HD)-LABA	ICS (HD) +montelukast
	6	ICS (HD)-LABA + OCS	ICS (HD) +montelukast+ OCS

Abbreviations: +, add this to another therapy; ±, with or without this additional therapy; HD, high dose; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic agonist; LD, low dose; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy; MD, medium dose; OCS, oral corticosteroid; SABA, short-acting beta$_2$-agonist; VLD, very low dose;

[a] This is intended as a brief overview of maintenance options for ongoing (not necessarily initial) regularly scheduled treatment; please refer to the respective guidelines for details.

[b] All patients should receive a reliever therapy regardless of whether they receive maintenance therapy. See Table 2 for reliever therapy recommendations.

[c] Although not always specified by guidelines, generally, maintenance therapies are to be administered every day (or multiple times per day) except for some biologic therapies. Refer to guidelines for additional details and dosing guidance by product type and age group and to section 5.1 of this report regarding intermittent ICS treatment

[d] The 2020 report is a targeted update to the original 2007 guideline. Recommended maintenance therapies in this table include those with evidence updated for the 2020 guideline (eg, ICS options), along with other therapies recommended in 2007 that were not considered for an evidence update; therefore, some treatments considered as options by the guideline may no longer be in favor based on recent evidence.

[e] Biologic therapy is neither a preferred or alternative option in the NAEPP 2020 guideline; it is an adjunctive option to be considered at treatment step 5 or step 6

5.0 CONSIDERATIONS FOR USING GUIDELINE-PREFERRED MAINTENANCE AND/OR RELIEVER THERAPIES

5.1 Maintenance therapy

Maintenance medications are recommended for most patients with asthma, with reliever-only regimens as an option for patients with less-severe symptoms and risk factors (see **Tables 2** and **3**). Guidelines provide a variety of options (preferred or alternative) so that treatment selection can be tailored based on patient preference, intolerances or allergies, affordability, comorbidities, and ability to administer the medication.[1,9] Nonetheless, there are some situations when only intermittent use of a maintenance therapy is an option, or where treatment with an ICS-containing medication (the preferred maintenance therapy for most patients) could be challenging, which are described below, in addition to some other considerations.

- *Intermittent ICS treatment:* There are some situations in which patients may only temporarily or intermittently fill "maintenance" medications, for example:
    - Intermittent ICS is conditionally recommended by the NAEPP (2020) for children aged ≤ 4 years with recurrent wheezing triggered by respiratory tract infections, instead of as-needed SABA monotherapy.[9] GINA considers intermittent high-dose ICS to be an alternative option for intermittent viral-induced wheezing in children ages 0-5 years (step 1 treatment). Episodic/as-needed ICS can also be considered for children ages 0-5 years with viral-induced wheezing during treatment step 2, although GINA prefers daily low-dose ICS treatment.[1]
    - For adolescents and adults with asthma triggered only by seasonal allergies (ie, asthma symptoms only occurring at a predictable time), as-needed ICS-formoterol or scheduled ICS (treatment step 2) may be given temporarily, only around the time of symptoms.[1] GINA also mentions the option of seasonal ICS use for young children with seasonal symptoms.[1]
    - As-needed ICS-formoterol and ICS-SABA (separately or as 1 inhaler) are reliever options according to guidelines (despite US-available ICS-formoterol and ICS-only inhalers not having FDA-approval as reliever therapy[26-28]); some patients with mild asthma may be managed with as-needed use of one of these therapies (see Table 2).[1,9]
- *Issues using the inhaler:* Patients who are unable to appropriately use an inhaler, including with assistive devices like a spacer and/or facemask, should not use that device. Maintenance medications are available as different types of inhalers or as solutions for nebulization, so a device usable by the patient/caregiver should be selected.
- *Select adverse effects or contraindications:*
    - Many DPIs are formulated with lactose and could be contaminated with milk proteins, so manufacturers recommend patients with severe cow's milk allergies avoid those inhalers (it is contraindicated).[29]
    - ICS-containing medications are well-tolerated by most patients, although the risk for adverse events increases with higher ICS doses.[1] Select warnings/precautions for ICS-containing medications include oral candidiasis, reduced bone mineral density, increased intraocular pressure, adrenal suppression, and reduced growth velocity.[26,30] Growth velocity should be monitored in children and the lowest effective ICS dose should be used.[1] Older adults, particularly those with comorbidities such as osteoporosis and/or glaucoma, may be at greater risk for some ICS-associated adverse events, but GINA does not specifically advise against using maintenance medications in older patients with asthma who require treatment.[1] Benefits of long-term high-dose ICS (a necessary treatment for few asthma patients) should be balanced against the potential risks.[1]
    - The LTRAs montelukast and zafirlukast are alternatives to ICS-containing maintenance therapy for children and adults with mild asthma, and options for adjunctive maintenance therapy to ICS for children and adults with moderate to severe asthma.[1] Montelukast carries a black box warning for serious neuropsychiatric events (eg, depression, suicidality, agitation), which should be considered before starting treatment.[31] Zafirlukast is contraindicated in patients with hepatic impairment and carries warnings/precautions for hepatotoxicity and neuropsychiatric events, among others.[32]
    - Strong cytochrome P450 inhibitors (eg, ketoconazole, ritonavir, erythromycin) can increase a patient's exposure to and risk of adverse effects from ICS and can also increase the risk for

adverse effects from LABAs salmeterol and vilanterol. GINA advises avoiding these medications concomitantly with ICS/ICS-LABA.[1]

5.2 Reliever Therapy with Inhaled Corticosteroids

ICS-formoterol is preferred over SABA reliever therapy for adolescents (≥ 12 years old) and adults (at all treatment steps per GINA or only at step 3-4 per NAEPP); and for children ages 6-11 is preferred (per NAEPP) or is an option (equally preferred to as-needed SABA) as MART for step 3 and 4 (per GINA).[1,9] Use of ICS whenever SABA is administered is also an equally preferred option, as with as-needed SABA only, for ages 12 and older at step 2 (per NAEPP); is the *preferred* option for ages 6-11 years at step 1 (per GINA); and is an *alternative option* (secondary to ICS-formoterol) along with as-needed SABA only use for ages 12 and older at all treatment steps (per GINA).[1,9] However, there are potential scenarios in which ICS-formoterol or ICS with SABA are inappropriate or not selected, including but not limited to the following:

- *Patient stability on alternative regimen:* Guideline recommendations should be individualized. For patients well-controlled on a treatment regimen of an ICS-containing maintenance medication with an as-needed SABA who have not had any recent exacerbation nor carry a high risk for exacerbations, continuation of their regimen is warranted.[9,33]
- *Patients already taking an ICS-LABA other than ICS-formoterol:* For patients established on another ICS-LABA for maintenance therapy who do not wish to change their maintenance treatment, ICS-formoterol should not be used as their reliever therapy due to a lack of evidence for using this combination[1] and the potential for harm.[33]
- *Generalizability concerns/lack of FDA indication:* The majority of RCT evidence for ICS-formoterol as MART and all evidence for as-needed reliever therapy used a budesonide-formoterol DPI,[1] which is not available in the US. In the US, budesonide-formoterol is available as a generic, branded generic (Breyna), or brand product (Symbicort) pressurized MDI inhaler (not DPI);[34] these products have not been FDA-approved for as-needed reliever use.[26,35] Other than budesonide-albuterol (Airsupra) that is an FDA-approved asthma reliever for ages 18 and older,[24] stand-alone ICS inhalers (eg, budesonide DPI [Pulmicort Flexhaler] and fluticasone DPI [Arnuity Ellipta]) are not FDA-indicated for as-needed use.[27,28] Thus, patients may have limited access to using ICS-containing products for as-needed use (despite guideline recommendation), if payers do not recognize the recommended off-label use and only allow quantity fills for maintenance therapy.
- *Limited evidence:* Less evidence is available for using ICS-formoterol as a reliever therapy in children under 12 years old, and there is a lack of evidence as reliever therapy during pregnancy.[33] According to GINA, evidence supporting the recommendation for as-needed ICS with SABA reliever therapy at treatment step 1 for ages ≥ 6 years is very limited; the step 1 recommendation is extrapolated indirectly from studies of children, adolescents, and adults at step 2 .[1]
- *Possible concerns with over-exposure to ICS or formoterol:* As-needed use of ICS-formoterol could result in over-exposure to ICS or formoterol if frequent use is required. It is recommended that patients aged 12 years or older not exceed 12 puffs daily (54 mcg of formoterol) and patients 4-11 years old not exceed 8 puffs daily (36 mcg formoterol) when used as reliever-only or MART.[9] Notably, some RCT evidence suggests (a) lesser cumulative ICS use when patients are treated with as-needed ICS-formoterol compared to using scheduled ICS with as needed SABA, and (b) that MART, compared to ICS or ICS/LABA with SABA, reduces the risk of exacerbations that potentially would have required treatment with oral corticosteroids thus reducing steroid exposure overall.[9,33] Therefore, corticosteroid-associated risks might be lessened in some patients treated with as-needed ICS-formoterol/MART compared to alternative regimens with scheduled ICS maintenance treatment and as-needed SABA.[9]
- *Adverse effects or contraindications:* ICS-formoterol should not be used by patients with an intolerance to it.[9] Budesonide-formoterol should not be used by people with a hypersensitivity to any component of the inhaler, or as the primary treatment for acute severe asthma.[26,35] Warnings/precautions to using budesonide-formoterol include those for ICS-containing medications (see adverse events in section 5.1 above), with select additional warnings for paradoxical bronchospasm, adverse effects in people with comorbidities sensitive to sympathomimetic amines (eg, diabetes mellitus, seizure disorders, thyrotoxicosis, cardiovascular disorders), and a risk of hyperglycemia and/or hypokalemia from $beta_2$-receptor agonism. Patients with conditions that could be aggravated by budesonide-formoterol should exercise increased caution.[26]

- *Issues using the inhaler:* Patients who are unable to appropriately use an inhaler, including with assistive devices like a spacer and/or facemask, should not use that device.

6.0 SABA UTILIZATION RESULTS

We identified 1,400 Utah Medicaid FFS patients with an asthma diagnosis and without a conflicting pulmonary diagnosis who filled at least 1 SABA prescription during the study period (10/1/2022 to 9/30/2023) and who had at least 2 qualifying months of Medicaid eligibility (ie, selected cohort).

Refer to **Appendix C** for a flow diagram showing selection of the patient cohort.

6.1 Total Cohort SABA Utilization

In the full selected cohort, the median duration of Medicaid eligibility was 9 months (range 6-11), and the mean (SD) number of SABA canister equivalents was **3.3** (3.9) during that time. Accounting for the number of reliever months after the first indexed SABA fill, the mean (SD) SABA canister equivalents filled per month was 0.42 (0.37), or approximately one every 2.4 months.

Overall, approximately 38.1% (533) of patients in the selected cohort filled 3 or more SABA cannister equivalents during the 1-year study period, meeting criteria for frequent SABA use. Only 4.2% of patients filled 12 or more SABA equivalents during the study period. Of the 533 patients who filled at least 3 SABA canister equivalents, most (41.1%) filled between 4 and 6 SABA canister equivalents.

Table 4 and **Appendix D, Table D1** contain additional descriptive statistics related to SABA utilization in the total patient cohort during the study period.

Table 4. Distribution of Utah Medicaid FFS Patients by Total SABA Canister Equivalents[a] Filled during the 1-year Study Period

Total SABA canister equivalents filled	Number of patients (n=1400)	Percentage of total patients
1-2	**867**	**61.93%**
≥ 3	**533**	**38.07%**
3	129	9.21%
4-6	219	15.64%
7-9	86	6.14%
10-11	40	2.86%
≥ 12	59	4.21%

Abbreviations: FFS, Fee-for-Service; n, number of patients; SABA, short-acting beta$_2$ agonists

[a]SABA canister equivalents filled is tallied from outpatient pharmacy claims for SABA inhaler and nebulizer products that were converted to 200-actuation SABA inhaler equivalents using formulas developed by product type (see Appendix A, Tables A2 and A3 for details).

6.2 Total Cohort Maintenance Therapy Utilization

Appendix D, Figure D1 provides the numbers of patients who filled an ICS-containing therapy, LTRA therapy, both, or neither during the study period. Of the total selected cohort (1400 patients), 27.1% filled a prescription for an ICS-containing therapy only, 8.9% filled a prescription for a LTRA only, and 5% filled a prescription for both maintenance therapy types. Most patients (68.9% of the study cohort) did not fill any ICS-containing or maintenance therapy during the study period.

6.3 SABA Utilization by Subgroup

The following sections report our descriptive analysis of the total SABA 200-actuation canister equivalents filled by subgroups of observational interval, age group, and maintenance therapy PDC.

6.3.1 Subgroup with ≥3 SABA Canister Equivalent Fills

Of the 533 patients (38% of the total selected cohort) who filled 3 or more SABA canister equivalents in the study period, 60% (321) did not fill an ICS-containing or LTRA medication.

6.3.2 SABA Utilization by Observation Interval

Table 5 shows descriptive statistics for the total SABA canister equivalents filled during the study period by observation interval, which is the number of months of Medicaid eligibility. Results suggest that the filled number of SABA canister equivalents is correlated with observational time: generally, as maximum observation interval increased, patients filled a greater number of SABA canister equivalents. The proportion of patients who filled ≥ 3 SABA canister equivalents increases by length of observation interval: within the shortest observation length of 2-3 months, only 10.1% patients filled ≥ 3 SABA cannister equivalents, whereas within the longest observation length of 12 months, 65.7% of people filled ≥ 3 SABA canister equivalents.

6.3.3 SABA Utilization by Age Group

Of the 1,400 selected cohort patients, 931 (66.5%) patients were adults ages 18+ years as of the index date (ie, date of first SABA prescription filled during the study period). Only 299 (21.4%) patients were 11 years of age or younger as of the index date.

Without accounting for differences in the observation interval, trends suggest that the frequency of SABA fills increases with age, with the biggest differences between those < 6 years versus other age brackets (see **Table 6**). The proportion of patients per age group filling ≥ 3 SABA cannister equivalents during the study period was 27% (age <6 years), 37% (6-11 years), and 39.5% (≥ 12 years).

6.3.4 SABA Utilization by Proportion of Observation Days Covered (PDC) with Maintenance Therapy

Of the total selected cohort, most patients (69%) did not fill any maintenance medication during the observation interval in the study period (see **Table 7**). The distribution of total SABA canister equivalents filled, mean/median for total SABA canisters equivalents filled, and SABA canister equivalents filled *per month* showed that SABA utilization tended to increase as maintenance therapy utilization increased. One exception is the subset of patients who filled maintenance medications at the lowest frequency (PDC >0% to <25%), for which the mean/median total SABA canister equivalents and proportion of patients filling ≥3 SABA canister equivalents were slightly less than that of the subset with no maintenance therapy (PDC 0%). The proportion of patients who filled ≥ 3 SABA equivalents was greatest among patients in the second highest maintenance PDC category of 25% to <75% (59.3%), followed closely by patients in the ≥75% maintenance PDC category (53.1%). The mean and median SABA cannister equivalents filled per month were highest among patients with the greatest maintenance medication utilization.

6.3.4.1 SABA Utilization by Subgroup among Patients with 0% PDC (without Maintenance Therapy)

Like the entire study population, most patients in each age group did not fill any maintenance therapies. The proportion of patients by age group without any maintenance therapy (0% PDC) during the observation period is as follows: <6 years old, 62.9%; 6-11 years old, 61.3%; and ≥12 years old, 69.8%.

Table 8 shows descriptive statistics for the total SABA canister equivalents filled, as well as SABA cannister equivalents filled *per observed months* by age and number of observation months among patients with 0% PDC for maintenance therapy. For each age group, the mean of total SABA canisters equivalents filled is highest among patients with the longest observation interval (12 months). Mean and median values of SABA canister equivalents filled per observed month tend to be highest at the extremes of observation interval length (2-3 months and 12 months) among patients <6 years old and ≥ 12 years old.

Refer to **Appendix D, Tables D2 and D3** for SABA utilization descriptive statistics for other PDC subgroups by age and observation interval.

Table 5. Total SABA Canister Equivalents[a] Filled[b] during the Observation Period and per Month, by Observation Interval Length

Range of observation interval months	Number of patients per range	Distribution of patients n (%) by total SABA canister equivalents filled per observational interval length[d]							Total SABA canister equivalents filled during observation		SABA canister equivalents filled *per observed month*	
		1-2	≥ 3	3	4-6	7-9	10-11	≥ 12	Mean (SD)	Median (25th–75th percentile)	Mean (SD)	Median (25th–75th percentile)
2-3	168	151 (89.9%)	17 (10.1%)	11 (6.6%)	6 (3.6%)	0 (0%)	0 (0%)	0 (0%)	1.49 (0.85)	1 (1.0–2.0)	0.63 (0.38)	0.50 (0.33–0.67)
4-6	256	209 (81.6%)	47 (18.4%)	25 (4.3%)	22 (8.6%)		0 (0%)	0 (0%)	1.79 (1.39)	1 (1.0–2.0)	0.36 (0.26)	0.25 (0.20–0.50)
7-9	343	207 (60.4%)	136 (39.7%)	38 (3.2%)	65 (19.0%)	17 (5.0%)	16 (4.7%)		2.96 (2.94)	2 (1.0–4.0)	0.37 (0.36)	0.23 (0.13–0.50)
10-11	344	201 (58.4%)	143 (41.6%)	37 (3.2%)	61 (17.7%)	28 (8.1%)	6 (1.7%)	11 (3.2%)	3.32 (3.24)	2 (1.0–4.2)	0.32 (0.31)	0.20 (0.10–0.40)
12	289	99 (34.3%)	190 (65.7%)	18 (3.8%)	69 (23.9%)	37 (12.8%)	22 (7.6%)	44 (15.2%)	6.18 (5.38)	5 (1.0–9.0)	0.52 (0.45)	0.42 (0.17–0.75)

Table 6. Total SABA Canister Equivalents[a] Filled[b] during the Observation Period and per Month, by Age Group

Age (years) as of index date[c]	Number of patients per age range	Distribution of patients n (%) by total SABA canister equivalents filled per age range[d]							Total SABA canister equivalents filled during observation		SABA canister equivalents filled *per observed month*	
		1-2	≥ 3	3	4-6	7-9	10-11	≥ 12	Mean (SD)	Median (25th–75th percentile)	Mean (SD)	Median (25th–75th percentile)
<6	126	92 (73.0%)	34 (27.0%)	11 (8.7%)	23 (18.3%)				2.17 (2.40)	1 (0.6–3.0)	0.29 (0.32)	0.18 (0.09–0.36)
6-11	173	109 (63.0%)	64 (37.0%)	26 (15.0%)	24 (13.9%)	6 (3.5%)	8 (4.6%)		2.89 (3.00)	2 (1.0–3.5)	0.37 (0.32)	0.29 (0.13–0.50)
≥ 12	1101	666 (60.5%)	435 (39.5%)	92 (8.4%)	177 (16.1%)	77 (7.0%)	36 (3.3%)	53 (4.8%)	3.53 (3.88)	2 (1.0–4.4)	0.44 (0.38)	0.33 (0.17–0.56)

Table 7. Total SABA Canister Equivalents[a] Filled[b] during the Observation Period and per Month, by Proportion of Days Covered (PDC) with Maintenance Therapy[e]

PDC range[f]	Number of patients per PDC range	Distribution of patients n (%) by total SABA canister equivalents filled per maintenance therapy PDC[d]							Total SABA canister equivalents filled during observation		SABA canister equivalents filled *per observed month*	
		1-2	≥ 3	3	4-6	7-9	10-11	≥ 12	Mean (SD)	Median (25th–75th percentile)	Mean (SD)	Median (25th–75th percentile)
0% (no MT)	965	644 (66.7%)	**321 (33.3%)**	81 (8.4%)	135 (14.0%)	48 (5.0%)	20 (2.1%)	37 (3.8%)	2.97 (3.37)	2 (1.0–3.8)	0.39 (0.34)	0.27 (0.14–0.50)
>0%–<25%	145	100 (69.0%)	45 (31.0%)	16 (11.0%)	18 (12.4%)	5 (3.4%)	6 (4.1%)		2.74 (3.07)	2 (1.0–3.0)	0.30 (0.30)	0.18 (0.13–0.36)
25%–<75%	209	85 (40.7%)	124 (59.3%)	23 (11.0%)	55 (26.3%)	25 (12.0%)	10 (4.8%)	11 (5.3%)	4.63 (4.11)	3.3 (1.5–6.1)	0.54 (0.38)	0.44 (0.29–0.67)
≥ 75%	81	38 (46.9%)	43 (53.1%)	9 (11.1%)	11 (13.6%)	8 (9.9%)	8 (9.9%)	7 (8.6%)	5.16 (5.55)	3 (1.0–7.0)	0.66 (0.54)	0.50 (0.25–0.92)

Abbreviations: MT, maintenance therapy; n, number of patients (count); PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists; SD, standard deviation.

*[a] SABA canister equivalents is a count of the approximate number of 200-acutuation SABA inhaler canisters filled over the study period (10/2022 to 9/2023) by each patient in the cohort, with inhaler canisters with fewer than 200 actuations and nebulizer products converted to 200-actuation SABA canister equivalents (see **Appendix A** for conversions and additional information)*

*[b] Fills are outpatient pharmacy prescription claims indicating that a patient picked up a SABA prescription. Each claim was converted to a count of 200-actuation SABA equivalents filled using a standard formula developed by product type (see **Appendix A**).*

[c] Index date is the date of the first SABA prescription filled during the study period.

[d] For patient privacy, we combined neighboring cells when one or more individual cell had a patient frequency <5.

[e] Maintenance therapies included oral leukotriene receptor antagonists (LTRAs) like montelukast and/or inhaled corticosteroid (ICS)-containing therapies identified by outpatient pharmacy claims during the study period.

[f] PDC defined as the % of observed days with maintenance therapy available (see methods in section 2.1.4)

Table 8. SABA[a] Utilization During the Observation Period and per Month, among Patients Receiving No ICS or Maintenance Therapy (0% PDC), by Subgroup Category

Subgroup category		Number (%) of patients per subgroup	Total SABA canister equivalents filled[c] during observation		SABA canister equivalents filled *per observed month*		
Age (years) as of index date	Range of observation interval months		Mean (SD) per subgroup	Median per subgroup (25th–75th percentile)	Mean (SD) per subgroup	Median per subgroup (25th–75th percentile)	95% confidence interval of the mean per subgroup
<6	**2-3**	11 (8.7%)	1.62 (1.11)	1 (1–2)	0.67 (0.48)	0.50 (0.33–1.0)	0.38–0.95
	4-6	14 (11.1%)	1.37 (2.20)	0.35 (0.25–1)	0.26 (0.38)	0.08 (0.05–0.17)	0.06–0.46
	7-9	24 (19.0%)	1.47 (1.64)	1 (0.25–1.65)	0.18 (0.20)	0.12 (0.04–0.22)	0.10–0.26
	10-11	30 (23.8%)	1.79 (1.26)	1.15 (1–2.5)	0.17 (0.12)	0.11 (0.09–0.23)	0.13–0.21
	12	11 (8.7%)	5.23 (4.85)	3 (1.2–9.25)	0.44 (0.40)	0.25 (0.10–0.77)	0.20–0.68
6-11	**2-3**	11 (6.4%)	1.38 (0.54)	1 (1–2)	0.60 (0.25)	0.5 (0.50–0.67)	0.45–0.75
	4-6	18 (10.4%)	1.80 (0.96)	2 (1–3)	0.39 (0.21)	0.4 (0.20–0.50)	0.29–0.48
	7-9	27 (15.6%)	2.32 (2.27)	1.6 (1–3)	0.31 (0.32)	0.22 (0.11–0.43)	0.19–0.43
	10-11	25 (14.4%)	3.09 (3.98)	2 (1–3.6)	0.29 (0.36)	0.2 (0.09–0.33)	0.15–0.43
	12	25 (14.4%)	4.68 (4.53)	2.8 (1–6.5)	0.39 (0.38)	0.23 (0.08–0.54)	0.24–0.54
≥ 12	**2-3**	104 (9.4%)	1.42 (0.71)	1 (1–2)	0.60 (0.30)	0.5 (0.42–0.67)	0.54–0.66
	4-6	157 (14.3%)	1.79 (1.38)	1 (1–2)	0.36 (0.26)	0.25 (0.20–0.50)	0.32–0.40
	7-9	183 (16.6%)	2.80 (2.70)	2 (1–4)	0.35 (0.34)	0.22 (0.13–0.44)	0.30–0.40
	10-11	180 (16.3%)	3.13 (2.92)	2 (1–4)	0.30 (0.27)	0.2 (0.10–0.40)	0.26–0.24
	12	145 (13.1%)	6.06 (5.33)	4.75 (2–9)	0.50 (0.44)	0.40 (0.17–0.75)	0.43–0.58

Abbreviations: ICS, inhaled corticosteroids; n, number of patients (count); PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists; SD, standard deviation.

6.3.5 Comparison of SABA Canister Equivalents Filled per Month

To account for differences in observation time between patients, we calculated the mean (SD) and median (range) SABA canister equivalents filled divided per months of observation for each subgroup, which allows for a comparison normalized to observation interval length (see **Tables 5-8** and **Appendix D** for details).

Among the subgroups of age, observation interval, and maintenance therapy PDC, the groups with the highest median and mean SABA canister equivalents *per month* are patients with 2-3 observation months and maintenance PDC ≥ 75%, both having medians of 0.50 canister equivalents/month, and means (SD) of 0.63 (0.38) and 0.66 (54), respectively. The median of 0.5 corresponds to filling approximately one SABA canister equivalent every 2 months.

7.0 CONSIDERATIONS FOR ASSESSING SABA USE WITH CLAIMS DATA

Limitations of assessing SABA use with pharmacy claims should be considered when interpreting and making decisions based on potential SABA "high-frequency use". Considerations for assessing SABA claims data include but are not limited to the following:

- *Claims may not reflect true medication usage:*
    - While patients tend to fill prescriptions once they are close to finishing their supply of a medication, pharmacy claims for a filled prescription do not always indicate true medication usage. Other reasons a refill may be needed aside from using the complete prior supply may include expiration of the product, early fill due to planned travel, improper storage or damaged product, convenience/practicality of having multiple inhalers at various locations, loss of the product, etc.
    - Particularly for children, patients may fill multiple SABA products for storage/use in multiple settings (eg, for home, school [ie, inhaler to remain in backpack], daycare, or other main caregiver location). Such dispensing may cause a patient to reach the 3+ canister equivalents threshold rapidly, as the 3rd canister fill may occur at the first occurrence of any one of their initial inhalers running out.
- *SABAs may be used to prevent exercise-induced asthma*
    - In addition to as-needed use for asthma symptoms, SABAs can be used before exercise to prevent EIB. When assessing past-month asthma control level, GINA recommends not routinely considering SABA use before exercise as part of assessing SABA use frequency.[1] While we excluded patients with an ICD-10 diagnosis code for EIB in the year prior to their first SABA claim to reduce confounding, patients in our cohort requiring frequent SABA use could have been appropriately using a SABA to prevent EIB (ie, it's possible the EIB diagnosis occurred at other times in their record or a claim for the code has yet to be entered in their record for other possible reasons).
    - Notably, the risk of EIB is reduced by ICS maintenance therapy, and possibly by pre-exercise and as-needed use of ICS-formoterol (lower quality evidence), so patients with asthma and EIB who are not using an ICS-containing treatment should be encouraged to do so. Patients using SABAs to prevent EIB more than once daily are also at risk for developing tolerance to its effects.[1]

8.0 CURRENT UTAH SABA QUANTITY LIMITS AND APPROACHES BY OTHER SELECT MEDICAID PROGRAMS

As of March 2024, the following SABAs are preferred on the Utah Medicaid Preferred Drug List (PDL): albuterol nebulizer (generic), levalbuterol nebulizer (generic), and pMDI branded albuterol inhalers, ProAir HFA, Proventil HFA, and Ventolin HFA. Other products are non-preferred. While there are not quantity limits for nebulized products, all SABA-only inhalers are limited to 2 inhalers/30 days and the albuterol-budesonide combination inhaler (a reliever product) is limited to 1 inhaler/30 days. No prior authorization is required other than for accessing a non-preferred SABA using the Medicaid Coverage Exception form.[36]

Many other asthma medications have preferred status on the PDL as of March 2024, providing access to ICS DPI inhalers or budesonide nebulizer, montelukast, and multiple ICS-LABA combination inhalers; however, quantity limits are in place for these with the limit being 1 inhaler dispensed per 30 days. Symbicort (budesonide-formoterol) is among preferred combination inhalers with a limit of 1 inhaler per

30 days. Budesonide-formoterol could be used off-label to fulfill guideline recommendations for as-needed ICS-formoterol reliever or MART, however some patients using it for either of these purposes may require more than the current restriction allows of 1 inhaler per month (potentially a barrier to using ICS-based guideline recommended reliever therapy).[9]

8.1 Other Medicaid Program's SABA Policies

Table 9 shows information about 5 other state Medicaid program policies for SABAs to determine whether other states have SABA-specific quantity limits, prior authorizations, and/or preferred status on the contract drug list (CDL) or PDL. Reviewed information primarily included state's CDL/PDL, and prior authorization criteria when available. All 5 reviewed states have at least 1 SABA product as preferred on the PDL: California, Oregon, Washington, Missouri, and New York.[37-41]

Only Missouri has SABA-specific quantity limits that were developed due to concerns about the association between frequent SABA use and asthma exacerbations in the medical literature. Excluding patients with cystic fibrosis, Missouri limits adults to 3 SABA-only inhaler canisters every 6 months, and limits patients of all ages to 120 SABA-only nebulizer vials every 2 months. The Missouri pharmacy program encourages prescribers to consider MART with ICS-formoterol (eg, Symbicort) as an alternative to SABA reliever therapy.[42]

In October 2023, the Oregon Medicaid program reviewed and discussed SABA utilization, and decided to implement (1) a one-time education intervention (fax to providers about SABA therapy for specific patients) and (2) retrospective drug utilization review fax to providers to notify them if a patient fills 3 SABA inhalers within 6 months, unless the patient has COPD. The Oregon committee discussed implementing a SABA quantity limit of 6 claims per 6 months, but decided against recommending it for reasons that were not documented.[43]

Table 9. Overview of Select Other Medicaid Program's SABA Policies

State	Quantity limit (QL)?	Population affected by QL	QL description	SABA-specific Prior Authorization	Notes
California	No[a]	NA	NA	Unknown, PA criteria not accessible.[44] No drug-specific PA required per CDL.[37]	• Includes preferred albuterol and levalbuterol inhalers or nebulizer products on CDL (2/2024)[37] • Offers a home-based preventative asthma education program for patients with uncontrolled asthma[45]
Missouri	**Yes**	Patients of all ages[b]	120 SABA-only vials for nebulization every 2 months[42]	No drug-specific PA[46]	• Includes preferred albuterol inhalers and nebulizer products on PDL, with levalbuterol non-preferred (2/2024)[38]
		Adults[b]	3 SABA-only inhaler cannisters every 6 months[42]		
New York	No[a]	NA	NA	No drug-specific PA.[47]	• Includes preferred albuterol inhalers and nebulizer products on PDL, with branded levalbuterol inhaler (Xopenex) also preferred and generic levalbuterol products including inhalers and solutions for nebulization non-preferred (2/2024)[39]
Oregon	No[a,c]	NA	NA	No drug-specific PA[48]	• Albuterol inhaler and vial for nebulization are preferred on PDL; non-preferred products not listed on PDL (2/2024).[40] • A proposed SABA quantity limit of 6 claims per 6 months was rejected by the committee in October 2023[43]
Washington	No[a]	NA	NA	No drug-specific PA[49]	• Albuterol inhaler and vial for nebulization are preferred on PDL, while levalbuterol products are non-preferred (2/22/2024).[41]

Abbreviations: CDL, contract drugs list; COPD, chronic obstructive pulmonary disease; DUE, drug use evaluation; NA, not applicable; PA, prior authorization; PDL, preferred drug list; RetroDUR, retrospective drug utilization review; SABA, short-acting beta$_2$ agonist; QL, quantity limit;

[a] No quantity limits according to information from the designated state's preferred/contract drugs lists, or (lev)albuterol-specific prior authorization(s).

[b] Missouri quantity limits do not apply to patients with cystic fibrosis. It appears that limits would apply to all other populations (eg, including patients with COPD); however, evidence cited supporting the SABA quantity limit is for patients with asthma.

[c] According to information about PDL-preferred products; it is unknown whether there are quantity limits for non-preferred products.

9.0 SUMMARY AND RECOMMENDATIONS

Asthma is a heterogeneous chronic pulmonary disorder of airway hyperresponsiveness and reversible airway obstruction that is typically caused by airway inflammation.[1,2] Approximately 5.5% of children and 9.7% of adults in Utah had asthma as of 2021.[4-6] While most patients with asthma are considered to have mild- to moderate-severity symptoms,[1,7] all patients with asthma are at risk for severe acute worsening of symptoms (eg, bronchoconstriction), which can be life-threatening and unpredictable.[1] Thus, it has been a standard-of-care to supply patients with a reliever (ie, rescue) therapy to have on hand in the event of shortness of breath/wheezing symptoms or asthma exacerbation.

Current guidelines recommend **reliever therapy for all patients regardless of disease severity,** with the preferred type of reliever dependent on the recommending guideline, the patient's age, and asthma treatment step (ie, level of treatment intensity); this includes the 2023 Global Initiative for Asthma (GINA)[1] and 2020/2007 US National Asthma Education and Prevention Program (NAEPP)[2,9] guideline. Reliever options include short-acting beta$_2$ agonists (SABAs), either as monotherapy or in combination with ICS; and ICS with the LABA, formoterol. SABAs are the preferred reliever for all children up to 11 years of age, with the exception of children aged 5/6 to 11 years with moderate asthma (step 3-4), for whom ICS-formoterol is preferred (NAEPP) or is an option (GINA) as single inhaler maintenance and reliever therapy (MART).[1,9] To encourage ICS use for mild asthma, GINA prefers SABA with ICS (ICS-SABA) as the reliever at treatment step 1 for children ages 6-11 years old.[1] For adolescents (aged ≥ 12 years) and adults, ICS-formoterol is the preferred reliever therapy (with SABA or SABA-ICS as an alternative) by GINA, and is the preferred option at treatment step 3-4 by NAEPP[**]. The NAEPP considers SABA monotherapy (ie, regimens without any as-needed ICS or maintenance therapy) a preferred option at step 1 of treatment for all ages, whereas it is only an option at step 1 for children ages 0-5 years old by GINA. When SABAs are recommended, guidelines are not specific to the type of SABA (ie, albuterol or levalbuterol).[1,9] Regarding the method of delivery, guidelines generally prefer that patients of all ages use inhalers over nebulizers, provided that they can effectively use them alone or in combination with a spacer with or without a facemask. Nebulizers remain an option for patients who cannot or who are unwilling to use an inhaler.[1,2]

Notably, despite guideline recommendations in favor of an ICS-containing reliever treatment in many scenarios,[1,9] other than for the inhaler albuterol-budesonide (Airsupra),[24] such use of ICS products as-needed is technically off label in the US, which possibly impedes access/use of ICS as part of reliever therapy (eg, as ICS-formoterol, or as stand-alone ICS inhaler with SABA for as-needed use). Refer to section 5 for considerations and limitations of using ICS-containing reliever therapy.

Maintenance therapy is recommended by GINA 2023 and the NAEPP 2020 for all patients with moderate to severe asthma and is an option for some patients with mild asthma (step 2).[1,9] Single products that can satisfy a complete guideline-recommended preferred or alternative maintenance regimen contain either an inhaled corticosteroid (ICS), or oral leukotriene receptor antagonist (LTRA; eg, montelukast). ICS-containing regimens, as ICS-only or ICS with other medications to intensify treatment (eg, long-acting beta$_2$ agonists [LABAs]), are the preferred maintenance treatment by GINA and NAEPP.[1,9] Because LTRA monotherapy has been shown to be less effective than regular ICS (A-level evidence),[1] LTRA *monotherapy* (ie, without any other maintenance agent) is recommended as an alternative maintenance therapy for treatment step 2.[1,9] Patients with seasonal allergy-induced asthma lacking symptoms during confined times of the year have the option to take maintenance medications intermittently during the allergy season only.[1]

Observational studies have demonstrated an increased risk of severe asthma exacerbations (eg, requiring oral corticosteroids, an emergency department visit, or hospitalization due to asthma) and/or mortality among pediatrics and adult patients with asthma who use SABA medications more frequently (a sign/symptom of uncontrolled asthma), including as SABA monotherapy or regimens combined with maintenance therapy.[11,18,21] The association between frequent SABA use and increased exacerbations is part of GINA's rationale for recommending that if SABAs are used for step 1 treatment, they should be used in combination with ICS for children and adults ages 6 or older. Guidelines recommend monitoring

[****] Note that ICS-formoterol reliever therapy is only addressed in a limited capacity (ie, only 6 pre-set questions were addressed) by the 2020 focused update to the 2007 NAEPP guideline. As-needed ICS-formoterol for treatment steps 1-2 or 5-6 was not addressed in the 2020 update, so it is unknown whether it would be recommended as preferred by the NAEPP at these treatment steps.

patient's recent SABA use as one indicator of poor asthma control and recognize an annual threshold of prescription fills for SABA inhalers (canisters) as a risk factor for exacerbations:

- Requiring a SABA for symptom relief ≥ 1 time/week (GINA; for age <6 years), ≥ 2 times/week (GINA; for age ≥ 6 years), or ≥ 3 times per week (NAEPP; all ages), is one potential sign of uncontrolled asthma symptoms.[2,9]
- Drawing from observational studies, GINA defines frequent SABA use as filling prescriptions for ≥ 3 SABA canisters (200-actuation) per year, roughly corresponding to daily or more use, as the threshold for an increased risk of exacerbations regardless of asthma severity or concomitant ICS treatment.[1]
- Dose-dependent increases in the risk for exacerbations and mortality is associated with SABA usage exceeding 3 canisters/year. The NAEPP (2007) advises that using ≥ 1 canister every 1-2 months (ie, 6-12 canisters/year) is a predictor of severe exacerbations,[2] while GINA describes that each incremental step up in annual SABA canister usage, from 3-5 then 6-10 and ≥ 11, is associated with increased mortality compared with using ≤ 2 canisters per year, regardless of asthma severity.[1,18]

We performed a retrospective review and descriptive analysis of past-year (October 2022 to September 2023) SABA utilization among Utah Medicaid Fee-for-Service (FFS) patients with an asthma diagnosis to identify the proportions of patients with frequent SABA prescription fills (≥ 3 SABA 200-actuation canister equivalents within 2-12 months). Using outpatient pharmacy prescription claims, we identified fills for SABA-only inhaled products (or the combination budesonide-albuterol), including inhaler or nebulizer products. The dispensed quantity of inhalers with fewer than 200 actuations and nebulizer products were converted to 200-actuation SABA canister equivalents. Included patients were those that filled at least 1 SABA prescription in the past 1 year, who had an ICD-10 diagnosis for asthma other than for exercise-induced asthma within the 12-months preceding the first SABA indexed claim but who lacked other conflicting chronic pulmonary diagnoses, and who had at least 2 months of Utah Medicaid eligibility during the study period (to have sufficient time to fill 3 or more SABA inhaler prescriptions). We identified outpatient prescription fills for GINA-recommended maintenance medications (or ICS-containing asthma therapy in general) and determined their intensity of use in terms of the proportion of days covered (PDC) based on the claim's day supply.

Our selected cohort included 1400 Utah FFS patients with asthma and a median duration of Medicaid eligibility of 9 months. Overall, 533 (38%) of patients filled ≥3 SABA canister equivalents during the study period and 59 of those patients (4.2% of total population) filled ≥ 12 canister equivalents.

- Frequency of SABA fills was correlated with observation interval length, with a numerically greater proportion of patients with 12 months of observation (n=289) filling ≥ 3 SABA canister equivalents (66%) compared to those with 2-3 months of reliever (n=168; 10% filled ≥ 3 SABA canister equivalents).
- Regarding age, the frequency of SABA fills tended to increase with age. Of the 126 patients <6 years old, 27% filled ≥ 3 SABA canister equivalents, compared with 37% of patients 6-11 years old (total n=173) and 39.5% of patients ≥ 12 years old (total n=1101). Refer to section 7 regarding scenarios, other than medication usage, that could influence the number of canisters filled (eg, filling multiple inhalers to have medication supply at home and school).
- Despite GINA recommending that most patients ≥ 6 years old with asthma receive an ICS-containing regimen (ie, as maintenance therapy or part of reliever therapy), most patients (69%) did not fill any GINA-recommended ICS-containing medication, or other guideline-recommended maintenance option (LTRA), and only 5.8% of patients had high utilization during the study period, with the PDC ≥ 75%. Among patients with frequent SABA use (who filled ≥3 SABA canister equivalents), 60% (321) did not fill any ICS or LTRA therapy. Yet, it is possible that some patients classified as "on maintenance" were using an ICS-containing product appropriately for as-needed use, which could have driven the proportions of patients per PDC group downward. But we believe that the use of ICS as needed is probably low due to the quantity limit on ICS inhalers including budesonide-formoterol and otherwise due to the inconvenience of using an additional stand-alone ICS product.
- Generally, SABA utilization increased as the intensity of ICS use/maintenance therapy increased. Fewer patients who did not fill any maintenance therapy filled ≥ 3 SABA canister equivalents (33% overall and median of 0.27 filled per month of observation) compared with patients with a maintenance PDC ≥ 75% (53% overall and median of 0.50 filled per month of observation). This goes along with the idea that more frequent SABA utilization could be marker of higher disease severity, in addition to uncontrolled disease. A similar proportion of patients in each age group did not fill any ICS/maintenance therapy (63% of those <6 years old, 61% of those 6-11 years old, and 70% of those

≥ 12 years old). Investigating patients without any maintenance therapy (PDC=0%) by age group and months of observation, we found that the highest mean and median SABA canister equivalents filled were at the extremes of observational interval length (2-3 months and 12 months) for each age group.

Methods for calculating SABA utilization varied and therefore limited direct comparability, but generally, the proportion of patients with frequent SABA use (≥ 3 cannisters) in our Utah Medicaid FFS cohort is comparable to other sources. The Missouri Medicaid program reported that >40% of patients with asthma filled ≥ 3 SABA inhalers in 2021, and 6% filled more than 12.[42] Quint et al (2022) reported 40% of US and international patients ≥12 years old filled ≥ 3 SABA canisters/year, comparable to the 38% of patients of all ages in our cohort.[11] We accounted for nebulized SABA usage, which could have inflated our SABA utilization percentages compared to the other sources; however, the fact that we measured SABA usage in patients with as little as 2 months of Medicaid eligibility could have decreased the proportion of patients with frequent SABA use. Quint et al only measured SABA use in patients with 12 months of observation.[11] Median SABA canister equivalents filled per month of observation in the Utah Medicaid cohort was 0.50 among patients with only 2-3 months of observation, suggesting that 50% of that population was on track to fill at least 6 canister equivalents per year, and total SABA usage in our cohort might be greater if all patients had 12 months of observation.

Limitations of our descriptive analysis should be considered when interpreting the results (refer to section 7). It is important to note that claims for prescriptions and diagnoses may not reflect true medication usage and the patient's complete diagnosis profile. We applied selective criteria for inclusion in our patient cohort; of over 6800 patients who filled a SABA prescription during the study period, only 1400 (20%) met our inclusion criteria, with most patients being excluded for not having an asthma diagnosis in the 12 months preceding their first SABA claim in the study period. Maintenance therapy PDC was calculated conservatively, assuming that the days' supply carried over for all ICS-containing medications and all LTRAs; however, this method does not account for possible changes between different ICS-containing medications and does not account for patients who may have been taking ICS-containing medication appropriately as-needed. Our analysis included maintenance medications filled during the observation interval; it is possible that patients, particularly those with a short observation length, filled ICS/maintenance therapies before Medicaid enrollment.

We randomly reviewed 5 other state Medicaid program's policies for SABA products (eg, prior authorization criteria, or quantity limits). To the best of our knowledge, of the 5 reviewed programs, only Missouri has implemented quantity limits for SABA products.[37-42,44,47-49] Missouri Medicaid limits adults without cystic fibrosis to 3 SABA-only inhaler canisters every 6 months, and limits patients of all ages without cystic fibrosis to 120 SABA-only nebulizer vials every 2 months.[43] While we did not systematically review meeting minutes for all 5 Medicaid programs, we are aware that Oregon considered SABA quantity limits at their October 2023 Pharmacy and Therapeutics Committee meeting (limit of 6 claims per 6 months), but this proposal was not approved by the committee.[43]

As of March 2024, preferred SABA-only products on the Utah preferred drug list (PDL) include albuterol and levalbuterol solutions, and several albuterol metered dose inhalers. Utah Medicaid currently has quantity limits of 2 inhalers per 30 days for SABA-only inhalers.[36]

9.1 Considerations for SABA Policies and/or Other Programs

Based on our descriptive analysis and recent guideline recommendations,[1] at least 38% of Utah Medicaid FFS patients in the past year are potentially at an increased risk for exacerbations based on frequency of SABA prescription fills.

Some FFS patients may also be candidates for a starting a guideline-recommended ICS-containing medication (for as-needed use with a SABA, as-needed ICS-formoterol, or maintenance therapy) or LTRA. We found that 69% of included patients did not fill any GINA guideline-recommended maintenance therapy or as-needed ICS; however, the lack of FDA-approval for ICS as needed (other than for budesonide-albuterol [Airsupra]) may be impeding implementation of GINA recommendations. We also acknowledge that SABA monotherapy (ie, without as-needed ICS/maintenance therapy) is the preferred treatment for patients in step 1 (per NAEPP)[9]; or at times may not be favorable on a case-by-case basis as described in section 5.0.

Utah Medicaid may consider implementing policies and/or other programs to monitor or educate about use of SABAs for asthma. The following are some options that the Utah Medicaid Drug Utilization Review (DUR) Board may consider recommending and/or discussing:

1. Implement a retrospective DUR to notify (eg, by fax) providers of patients with asthma who fill some threshold of SABA canister equivalents within a designated time frame.
    a. Providers who prescribed a SABA to an at-risk patient (ie, those who exceeded a certain SABA threshold within a particular timeframe, as indicated by pharmacy claims) could be notified to evaluate whether changes to the patient's medication regimen is needed at the following patient visit (eg, by inquiring into the patient's actual SABA usage, and evaluating the patient's asthma control, other risk factors for exacerbations, inhaler technique, and adherence).
    b. The GINA 2023 guideline and observational studies point to filling ≥ 3 SABA canisters within 12 months as a risk factor for asthma exacerbations regardless of asthma severity and maintenance therapy.[1,18] SABA utilization exceeding 3 canisters (versus fewer) within a 12-month period is associated with an increased risk of asthma exacerbations, and possibly, mortality.[1,11,18,20,21]
    c. An arbitrary threshold for the number of prescriptions filled within a specific time frame could be selected to balance feasibility and promptness, which should be set at ≥ 3 SABA canister equivalents within at least 2 months and up 12 months. For example, Oregon Medicaid selected to alert prescribers once a patient fills at least 3 SABA inhalers within 6 months.[43]
        i. The selected timeframe may also consider the frequency at which providers commonly see patients. Frequency of provider visits may depend on many factors, such as patient/provider availability, symptom severity, and/or asthma control. The NAEPP advises that providers generally assess response 2-6 weeks after an increase in treatment and wait for at least 3 consecutive months of good control before stepping down treatment.[9] Depending on when the patient is able to secure an appointment with their provider, it could take months until the patient's next appointment, during which a review of their utilization and potential medication changes would occur.
    d. Our retrospective review measured SABA nebulizer solution and inhaler utilization, converting nebulizers and smaller inhalers to 200-actuation canister equivalents (see Table A2 for calculations). Calculating canister equivalents on an ongoing basis for the entire Medicaid population might be difficult to implement. For feasibility purposes, SABA utilization could track only the number of SABA inhaler canisters filled.
2. Implement a retrospective DUR to notify (eg, fax) providers of patients with asthma who may be a candidate for maintenance therapy, or reliever therapy including ICS.
    a. Since SABA monotherapy (ie, use without ICS as-needed or scheduled) is not recommended for patients ≥6 years old by GINA and is only an option at step 1 of therapy by the NAEPP,[1,9] some patients in the Utah Medicaid population who are not filling ICS or LTRA therapy may be candidates for maintenance therapy and/or reliever therapy incorporating ICS (ie, ICS-formoterol or ICS-SABA)[††].
    b. Most patients (67%) who did not fill any ICS/maintenance therapy had lower SABA utilization (filled 1-2 SABA canisters). Among patients with frequent SABA use (who filled ≥3 SABA canister equivalents), 60% (321) did not fill any ICS or LTRA therapy. Since those filling ≥3 SABAs are at increased risk for an exacerbation,[1,11,18,20,21] a retrospective DUR could prioritize targeting the prescribers for those patients with frequent SABA use and without ICS and/or maintenance therapy in that category first.
3. Perform educational outreach to providers and/or patients about the risks associated with SABA overreliance and/or to promote other best practices in asthma care.
    a. Utah Medicaid may consider educational outreach to patients filling ≥ 3 SABA canisters and/or prescribers in general. While patients should not be discouraged from SABA use, it may be helpful to provide patients and/or prescribers with information about how changes in the frequency of SABA usage (eg, 50-100% increase from baseline),[22] or requiring relief ≥ 2 times weekly (other than for use before exercise) in patients 6 years of ages or older,[1] could be signs of an exacerbation and/or poor asthma control.

[††] Despite guideline recommendations for ICS-containing reliever therapy for some patients, there are some challenges to initiating these therapies (refer to section 5.0). One limitation is the lack of FDA indication for most products. ICS-formoterol formulations available in the US (eg, Symbicort) are not FDA-approved for reliever therapy. Budesonide-albuterol (Airsupra) is the only combination ICS-SABA product available, and it is FDA-indicated for as-needed asthma reliever therapy for ages ≥ 18 years old. To the best of our knowledge, stand-alone ICS inhalers are not FDA-indicated for as-needed use.

b. Since 2002, Utah Department of Health and Human Services (DHHS) has housed the Utah Asthma Program (https://asthma.utah.gov/), committed to improving the well-being of Utahns affected by asthma. One aspect of this program is communicating and supporting people with asthma.[50] Utah Medicaid may consider collaborating with the Utah Asthma Program for educational initiatives.

c. It is important to highlight that if Utah Medicaid encourages prescribers to consider ICS-formoterol (as a reliever or MART) as an alternative to SABA reliever therapy, measures should be taken to guarantee patient access. Currently, budesonide-formoterol is a preferred product on the Utah PDL, but utilization is limited to 1 inhaler/month,[36] which might be a barrier to some patients using it as MART or reliever-only therapy (off-label, guideline-supported uses) who could require >1 inhaler/month with appropriate use.[9] The quantity limit of 1 inhaler/month for budesonide-albuterol (non-preferred on the PDL) and ICS-only inhalers (preferred on the PDL)[36] may also be a barrier to guideline-recommended as-needed use of ICS-SABA (as 1 inhaler or 2 separate inhalers) reliever therapy (although ICS-only inhalers are also not FDA-approved for reliever therapy).

4. Quantity limits for SABA products

a. Although an overreliance on SABAs to relieve symptoms increases the risk for poor asthma outcomes, SABAs are still a potentially life-saving medication for acute bronchoconstriction.[1] To reduce the risk of poor outcomes among patients with uncontrolled asthma, the priority could be placed on interventions listed above that focus on optimizing the patient's reliever regimen (eg, adding as-needed ICS for use with SABA or switching to ICS-formoterol) and/or maintenance regimen, rather than restricting access to the patient's rescue therapy (ie, reliever therapy). If it is desired to have stricter quantity limits, they should be implemented very cautiously, and should accommodate (or exclude from the restriction) certain patient populations (eg, patients with cystic fibrosis, EIB, or COPD).

b. Also consider that not all patients who fill prescriptions for SABAs will use the entire filled amount prior to a request for the subsequent fill. For example, some patients might fill multiple SABA inhalers within a short timeframe to have an inhaler available in multiple settings (eg, home, school, work, other caregiver location, etc.). Refer to section 7.0 for additional scenarios in which a patient might fill SABAs more frequently (eg, for prevention of EIB).

c. Utah Medicaid currently has quantity limits of 2 inhalers per 30 days (ie, up to 24/year) for SABA-only inhalers.[36] Missouri elected to limit SABA quantities in patients without cystic fibrosis to 3 SABA-only inhalers every 6 months in adults, and 120 SABA-only vials every 2 months regardless of age.[42] Oregon considered a less restrictive option of limiting patients without COPD to 6 claims per 6 months but opted not to implement quantity limits overall on rescue therapy, and instead implemented provider outreach initiatives.[43]

d. Recent asthma guidelines recommend monitoring SABA utilization, and considering it as one *of several* factors to guide appropriate treatment.[1,2] While guidelines highlight concerns with higher frequency SABA use as a marker of uncontrolled asthma and poorer outcomes, at no point do they advise or imply restricting access to a patient's reliever therapy after a particular threshold of use. Rather, recommendations imply optimizing the treatment regimen (eg, adding maintenance therapy and/or using a different reliever).[1,2,9] Moreover, other experts recommend that providers monitor the frequency of SABA fills and consider treatment changes based on that information, but not to refuse SABA fills in patients who are using them frequently.[22]

   i. **All patients with asthma are at risk for exacerbations, thus reliever medications are indicated for all patients to always have on hand.**

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APPENDIX A – ADDITIONAL METHODS

Tables A1-A3 below elaborate on methods used for our retrospective review and descriptive analysis.

Table A1. Criteria and Definitions for Inclusion in the Study Cohort[a]

Criterion	Definition and/or Source
Inhaled SABA	*Outpatient pharmacy claim for at least 1 of the following inhalers or products for nebulization during the study period (October 2022 to September 2023):* • Albuterol sulfate (mono-ingredient) with inhaled route of administration • Albuterol sulfate-budesonide (Airsupra) • Levalbuterol hydrochloride (HCl) • Levalbuterol tartrate The first SABA claim during the study period is the *index date.*
Asthma diagnosis[a]	*At least 1 inpatient or outpatient medical claim with an ICD-10 code for asthma other than exercise-induced asthma including within the 12 months preceding the index date:* • J45.2, J45.20, J45.21, J45.22, J45.3, J45.30, J45.31, J45.32, J45.4, J45.40, J45.41, J45.42, J45.5, J45.50, J45.51, J45.52, J45.9, J45.90, J45.901, J45.902, J45.909, J45.99, J45.991, J45.998, or J82.83 (eosinophilic asthma)
Conflicting chronic pulmonary diagnosis[b]	*At least 1 inpatient or outpatient medical claim with an ICD-10 code for one or more of the following conflicting pulmonary diagnoses anytime between the 12 months preceding the index date and the end of follow-up (end of the study period or Medicaid coverage):* • Simple and mucopurulent chronic bronchitis: J41.X • Unspecified chronic bronchitis: J42.X • Emphysema: J43.X • Other chronic obstructive pulmonary disease (including for asthma and COPD): J44.XX • Bronchiectasis: J47.X • Exercise-induced bronchospasm: J45.990 • Cystic fibrosis: E84.XX • Alveolar proteinosis: J84.01 • Pulmonary alveolar microlithiasis: J84.02 • Pulmonary fibrosis, unspecified: J84.10 • Idiopathic pulmonary hemosiderosis: J84.03 • Lymphangioleiomyomatosis: J84.81 • Other interstitial pulmonary diseases with fibrosis: J84.1 • Interstitial pulmonary disease, unspecified: J84.9 • Other specified interstitial pulmonary diseases: J84.8, J84.89 • Idiopathic pulmonary fibrosis: J84.114 • Coal worker's pneymoconiosis: J60 • Pneumoconiosis due to asbestos and other mineral fibers: J61 • Pneumoconiosis due to dust containing silica: J62.X • Pneumoconiosis due to inorganic dusts: J63.X • Unspecified pneumoconiosis: J64 • Pneumoconiosis associated with tuberculosis: J65

Table A1. Criteria and Definitions for Inclusion in the Study Cohort[a]

Criterion	Definition and/or Source
	• Airway disease due to specific organic dust: J66.X • Hypersensitivity pneumonitis due to organic dust: J67.X • Respiratory conditions due to inhalation of chemicals, gases, fumes, and vapors: J68.X *except for* J68.3 (subacute and acute) • Pneumonitits due to solids and liquids: J69.X • Respiratory conditions due to other external agents: J70.X *except for* J70.0, J70.2 (acute-specific conditions)
Medicaid eligibility	*Patient has Medicaid eligibility for 2 or more months during the follow-up period (month of the index date to 9/30/2023)*

Table A2. Cannister Equivalents Calculation

Product Type	Description	Calculation of Cannister Equivalents
Inhalers with 200 actuations	All albuterol or levalbuterol inhalers except for the inhaler with 60 actuations (listed below)	• Number of inhaler canisters logic: ○ If dispensed drug quantity > package size, the number of canisters dispensed is equal to the drug quantity divided by the package size rounded to the nearest integer (eg, round down for value <1.49 and round up for value ≥ 1.50) ○ If dispensed drug quantity ≤ package size and drug quantity ≠2, the number of canisters dispensed is 1 ○ If dispensed drug quantity ≤ package size and drug quantity = 2, the number of canisters dispensed is 2 • Number of canister equivalents (NCE): ○ NCE = number of inhaler canisters
Inhalers with 60 actuations	Ventolin HFA 8-gram canister (NDC 0173-0682-24)	• Number of inhaler canisters logic: ○ Use same calculations as for 200-actuation inhalers (above) • Number of canister equivalents (NCE): ○ NCE = number of inhaler canisters divided by 3.33, and rounded to the nearest 100th
Solutions for nebulization, single-dose vials	All albuterol or levalbuterol solutions except for the multi-dose albuterol solution (listed below)	• Number of vials logic: ○ If dispensed drug package size = 3 mL, the number of vials dispensed is equal to the drug quantity divided by the package size ○ If dispensed drug package size = 30 mL, the number of vials dispensed is equal to the drug quantity ○ If the dispensed drug package size = 1 mL, the number of vials dispensed is equal to the drug quantity • Number of canister equivalents (NCE): ○ NCE = number of vials divided by 100 and rounded to the nearest 100th
Solutions for nebulization, multi-dose container	Albuterol sulfate concentrate (2.5 mg/0.5 mL) solution, 20 mL bottle (NDC 5038-3074-20)	• Number of vials logic: ○ If the dispensed drug package size = 20 mL, the number of vials dispensed is equal to 40 • Number of canister equivalents (NCE): ○ NCE = number of vials divided by 100, and rounded to the nearest 100th

Abbreviations: NCE, number of canister equivalents; NDC, National Drug Code; SABA, short-acting beta$_2$-agonist

Table A3. Definitions for Descriptive Analysis

Criteria	Definition
Frequent SABA use	Pharmacy claims for ≥ 3 canister-equivalents of inhaled SABA products during the study period
SABA canister or canister-equivalent	• 1 SABA canister or canister-equivalent is defined as: ○ 1 albuterol or levalbuterol inhaler (200-actuation) – all inhalers except for *Ventolin HFA (albuterol sulfate) 8-gram canister* ○ 3 albuterol inhalers (60-actuation) – for *Ventolin HFA 8-gram canister only* ○ 100 vials of single-use albuterol or levalbuterol solution for nebulization ▪ See calculations in Table A2 for details
Maintenance therapy[a]	Maintenance therapy options were identified from the "antiasthmatic and bronchodilator" category of the Utah Medicaid AHFS medication list. Medications were classified into the following categories based on the active ingredient: • ICS-containing therapies: ○ Medications of the "steroid inhalants" and "adrenergic combinations" classes including ICS-only (except for triamcinolone acetonide and dexamethasone sodium phosphate), ICS-LABA, or ICS-LABA-LAMA inhalers, or solutions/suspensions for nebulization. • Leukotriene receptor antagonists (LTRAs): ○ All medications of this subclass, including montelukast or zafirlukast
Proportion of days covered (PDC)	PDC was calculated for maintenance therapies using the following: • Numerator = Total number of days during months with Medicaid eligibility between the index date and end of follow-up (9/30/2023) that the patient had at least 1 maintenance medication on hand • Denominator = The patient's total number of days with Medicaid eligibility during the study period Fills for ICS/maintenance medications were identified from outpatient pharmacy claims; we assumed that patients continued their maintenance medications during any inpatient stay. The outpatient prescription's days' supply was used to determine the number of days the patient had that medication on hand, and the prescription fill date identified when the day's supply started. Prescription fills were grouped by medication class into ICS-containing therapies or LTRAs (as described above). If the days' supply between prescription fill dates overlapped, any remaining days with medication on hand from earlier prescriptions were carried forward if the consecutive fills were for medications within the same category (LTRA or ICS-containing therapy). If overlapping prescriptions were for an ICS-containing therapy and LTRA, any overlapping days with both medication types on hand were counted toward the days' supply only once. Days with the maintenance medication available only contributed to the numerator during times when the patient had Medicaid eligibility.

Abbreviations: AHFS, American Hospital Formulary Service; ICS, inhaled corticosteroid; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; PDC, proportion of days covered; SABA, short-acting beta$_2$-agonist

[a] *We refer to all ICS-containing medications as "maintenance" therapy here for simplicity. Some ICS-containing medications (ie, ICS-formoterol, ICS-SABA, or ICS for use as-needed whenever a SABA is used) could be used as-needed as part of a guideline-recommended reliever regimen.*

APPENDIX B – GINA (2023) DEFINITION AND RECOMMENDED TREATMENT FOR ASTHMA EXACERBATIONS

For adults and children aged 6 years or older[1]:

- An asthma exacerbation is the progressive worsening of a patient's typical asthma symptoms to a magnitude warranting changes (eg, increased use of ICS therapy) to the patient's standard maintenance and/or reliever regimen.
- Exacerbations can be self-managed according to provider's instructions (an asthma action plan) and/or require treatment in a healthcare setting, depending on exacerbation severity. Self-managed treatment of an exacerbation according to an asthma action plan typically includes increased use of the patient's designated reliever (ie, ICS-formoterol, SABA, or ICS-SABA) and maintenance therapy (or initiating ICS therapy). Oral corticosteroids (OCS) may be initiated for patients with severe worsened symptoms or an insufficient response to increased reliever and ICS therapy after 2-3 days[‡‡].
- In healthcare settings, SABAs at an increased dose than for typical use are a primary treatment for exacerbations, in combination with oxygen and systemic corticosteroids. According to GINA, inhaled albuterol "…is the usual bronchodilator in acute asthma management" (page 153), including for treatment in primary care, emergency departments, or hospitals.

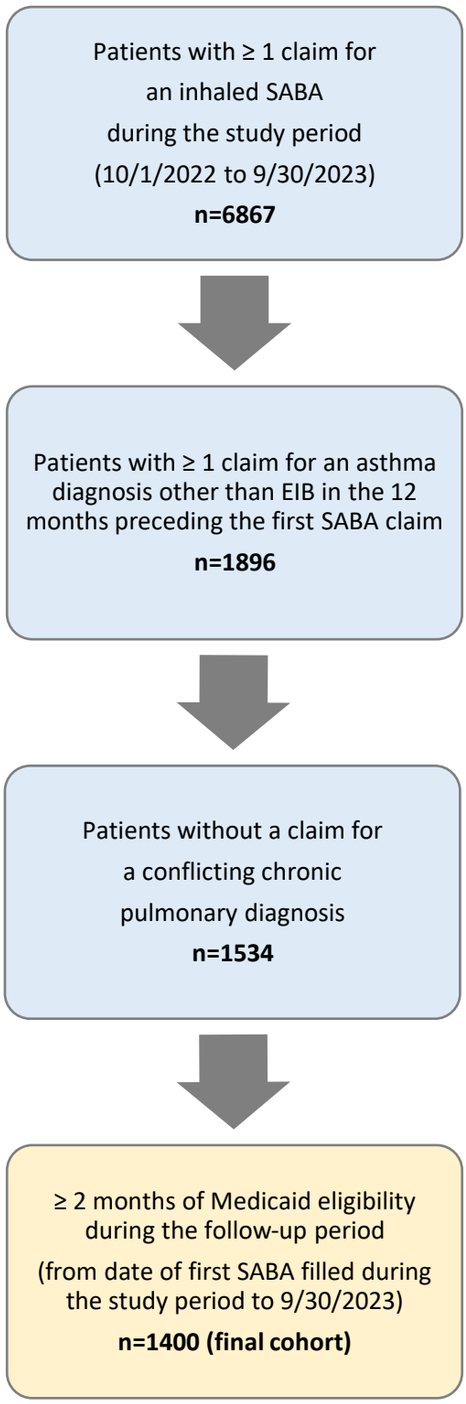
For children under 6 years old[1]:

- An asthma exacerbation is any worsening of symptom control of a magnitude to cause distress and require treatment by a healthcare provider or treatment with systematic corticosteroids. (Yet self-management of children without severe distress in this age group is implied based on GINA statements regarding the management of exacerbations when the child responds well to SABAs, such as children who require treatment with fewer than 6 SABA inhalations within 2 hours and recover within 24 hours).
- Exacerbations should be treated by SABAs, initiated at home followed by monitoring and/or going to the emergency room or outpatient provider, depending on severity and asthma action plan instructions from the provider. Children with distressing symptoms (eg, lack of response to inhaled bronchodilator) should be taken to a healthcare provider immediately. In a healthcare setting, exacerbations are managed with high-dose inhaled SABAs (typically albuterol) and oxygen, with OCS added to treatment in non-ambulatory settings.

[‡‡] It is unclear if GINA intends the guidance summarized in this paragraph about self-management of asthma exacerbations to be applied to adolescents and adults only, or to also be applied to children 6-11 years old. While it is not clear, it is likely that the general self-management principles apply to children ≥ 6 years old and adults.

APPENDIX C – UTAH MEDICAID PATIENT COHORT DISPOSITION

The flow chart below shows the selection of Utah Medicaid FFS patients included in our patient cohort. Inclusion criteria were applied in the order shown in the diagram. While 6,967 patients filled at least 1 SABA prescription during the study period, only 1400 patients met all criteria. Refer to **Appendix A, Table A1** for details about the patient cohort criteria.



APPENDIX D – ADDITIONAL RESULTS

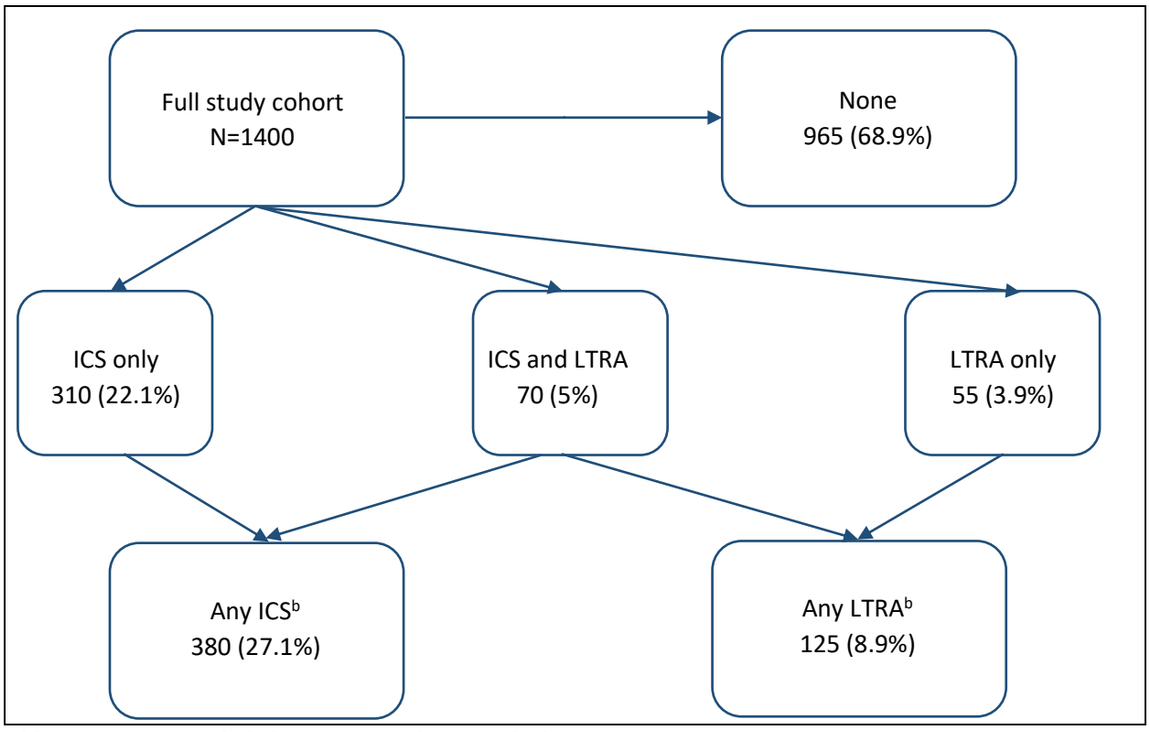
Table D1. Descriptive Statistics for SABA Canister Equivalents Filled[a] and Observation Interval Length in the Utah Medicaid FFS Patient Cohort (n=1400)

	Duration of Medicaid eligibility	SABA canister equivalents filled	SABA canister equivalents filled per *observed month*
Mean (SD)	8.24 (3.25)	3.3 (3.9)	0.42 (0.37)
Median (25^{th}–75^{th} percentile)	9 (6–11)	2 (1–4)	0.32 (0.15–0.53)

Abbreviations: FFS, Fee-for-Service; n, number of patients; SABA, short-acting beta$_2$ agonists; SD, standard deviation

[a]SABA canister equivalents filled is from outpatient pharmacy claims for SABA inhaler and nebulizer products that were converted to 200-actuation SABA inhaler equivalents using formulas developed by product type (see Appendix A Table A2 for details).

Figure D1. Maintenance Therapy Use[a] by the Study Cohort (n=1400) in the Study Period



Abbreviations: ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist;

[a] Maintenance therapy is defined at least 1 outpatient prescription claim for any days' supply during the study period.

[b] Maintenance therapies were grouped into ICS-containing (ie, ICS monotherapy, ICS-LABA, or ICS-LABA-LAMA) inhaler or nebulizer solution treatments, and LTRA (ie, montelukast or zafirlukast) treatments.

Table D2. Mean and Median SABA Canister Equivalents Filled, for Total Cohort and by Age, Observation Interval Length, and PDC Subgroups

Subgroup category	Mean (SD)	Median (25th–75th percentile)
Total Utah Medicaid FFS cohort (n=1400)		
NA	0.42 (0.37)	0.32 (0.15–0.53)
Age group		
<6 years	0.29 (0.32)	0.18 (0.09–0.36)
6-11 years	0.37 (0.32)	0.29 (0.13–0.50)
≥ 12 years	0.44 (0.38)	0.33 (0.17–0.56)
Observation interval length		
2-3 months	0.63 (0.38)	0.50 (0.33–0.67)
4-6 months	0.36 (0.26)	0.25 (0.20–0.50)
7-9 months	0.37 (0.36)	0.23 (0.13–0.50)
10-11 months	0.32 (0.45)	0.20 (0.10–0.40)
12 months	0.42 (0.37)	0.42 (0.17–0.75)
Maintenance therapy PDC (%)[a]		
0% (no maintenance therapy)	0.39 (0.34)	0.27 (0.14–0.50)
>0% to <25%	0.30 (0.30)	0.18 (0.13–0.36)
25% to <75%	0.54 (0.38)	0.44 (0.29–0.67)
≥ 75%	0.66 (0.54)	0.50 (0.25–0.92)

Abbreviations: FFS, Fee-for-Service; n, number of patients; PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists

[a] Maintenance therapies included oral leukotriene receptor antagonists (LTRAs) like montelukast and/or inhaled corticosteroid (ICS)-containing therapies identified by outpatient pharmacy claims during the study period.

Table D3. SABA Canister Equivalents Filled, by Age, Observation Interval Length, and PDC Subgroups

Subgroup category			Number of patients per subgroup (n)	Total SABA canister equivalents filled during observation range[a]		SABA canister equivalents filled *per observed month*[a]		
Age (years) as of index date	**Range of observation interval lengths**	**Maintenance therapy PDC (%)**		**Mean (SD) per subgroup**	**Median per subgroup (25th–75th percentile)**	**Mean (SD) per subgroup**	**Median per subgroup (25th–75th percentile)**	**95% confidence interval of the mean per subgroup**
<6	**2-3**	**0%**	11	1.62 (1.11)	1 (1–2)	0.67 (0.48)	0.50 (0.33–1.0)	0.38–0.95
		>0% to <25%	0	NA	NA	NA	NA	NA
		25% to <75%	5	1.60 (0.89)	1 (1–2)	0.63 (0.50)	0.33 (0.33–0.67)	0.19–1.08
		≥ 75%	0	NA	NA	NA	NA	NA
	4-6	**0%**	14	1.37 (2.20)	0.35 (0.25–1)	0.26 (0.38)	0.08 (0.05–0.17)	0.06–0.46
		>0% to <25%	<5	NC	NC	(NC	NC	NC
		25% to <75%	<5	NC	NC	NC	NC	NC
		≥ 75%	0	NA	NA	NA	NA	NA
	7-9	**0%**	24	1.47 (1.64)	1 (0.25–1.65)	0.18 (0.20)	0.12 (0.04–0.22)	0.10–0.26
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	6	3.25 (3.60)	1.6 (1–5.45)	0.38 (0.39)	0.23 (0.13–0.61)	0.07–0.69
		≥ 75%	0	NA	NA	NA	NA	NA
	10-11	**0%**	30	1.79 (1.26)	1.15 (1–2.5)	0.17 (0.12)	0.11 (0.09–0.23)	0.13–0.21
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	<5	NC	NC	NC	NC	NC
		≥ 75%	0	NA	NA	NA	NA	NA
	12	**0%**	11	5.23 (4.85)	3 (1.2–9.25)	0.44 (0.40)	0.25 (0.10–0.77)	0.20–0.68
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	9	3.52 (2.52)	3 (1.25–6.25)	0.29 (0.21)	0.25 (0.10–0.52)	0.16–0.43
		≥ 75%	0	NA	NA	NA	NA	NA
6–11	**2-3**	**0%**	11	1.38 (0.54)	1 (1–2)	0.60 (0.25)	0.5 (0.5–0.67)	0.45–0.75
		>0% to <25%	0	NA	NA	NA	NA	NA
		25% to <75%	<5	NC	NC	NC	NC	NC
		≥ 75%	<5	NC	NC	NC	NC	NC

Abbreviations: FFS, Fee-for-Service; n, number of patients; NA, not applicable; NC, not calculated; PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists;

[a] For subgroups with fewer than 5 patients, we did not calculate descriptive statistics

Table D3. SABA Canister Equivalents Filled, by Age, Observation Interval Length, and PDC Subgroups

Subgroup category			Number of patients per subgroup (n)	Total SABA canister equivalents filled during observation range[a]		SABA canister equivalents filled *per observed month*[a]		
Age (years) as of index date	**Range of observation interval lengths**	**Maintenance therapy PDC (%)**		**Mean (SD) per subgroup**	**Median per subgroup (25th–75th percentile)**	**Mean (SD) per subgroup**	**Median per subgroup (25th–75th percentile)**	**95% confidence interval of the mean per subgroup**
	4-6	**0%**	18	1.79 (0.96)	2 (1–3)	0.39 (0.21)	0.4 (0.2–0.5)	0.29–0.48
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	<5	NC	NC	NC	NC	NC
		≥ 75%	<5	NC	NC	NC	NC	NC
	7-9	**0%**	27	2.32 (2.28)	1.6 (1–2)	0.31 (0.32)	0.22 (0.11–0.43)	0.19–0.43
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	7	4.01 (2.90)	3 (2–6)	0.53 (0.37)	0.43 (0.25–0.86)	0.25–0.80
		≥ 75%	<5	NC	NC	NC	NC	NC
	10-11	**0%**	25	3.10 (3.98)	2 (1–3.6)	0.29 (0.36)	0.2 (0.09–0.33)	0.15–0.43
		>0% to <25%	18	2.01 (1.56)	1.25 (1–2)	0.19 (0.14)	0.12 (0.1–0.2)	0.12–0.25
		25% to <75%	5	4.86 (2.21)	5.3 (2–6.5)	0.47 (0.21)	0.53 (0.4–0.64)	0.28–0.66
		≥ 75%	<5	NC	NC	NC	NC	NC
	12	**0%**	25	4,68 (4.53)	2.8 (1–6.5)	0.39 (0.38)	0.23 (0.08–0.54)	0.24–0.54
		>0% to <25%	7	3.04 (2.27)	2 (1–5.4)	0.25 (0.19)	0.17 (0.08–0.45)	0.11–0.39
		25% to <75%	7	3.71 (2.74)	3.5 (1.5–5)	0.31 (0.23)	0.29 (0.13–0.42)	0.14–0.48
		≥ 75%	<5	NC	NC	NC	NC	NC
12	**2-3**	**0%**	104	1.42 (0.71)	1 (1–2)	0.60 (0.30)	0.5 (0.42–0.67)	0.54–0.66
		>0% to <25%	<5	NC	NC	NC	NC	NC
		25% to <75%	13	1.35 (0.90)	1 (1–1)	0.53 (0.32)	0.5 (0.33-0.5)	0.35–0.70
		≥ 75%	16	1.84 (1.37)	1 (1–2)	0.88 (0.64)	0.5 (0.5–1)	0.57–1.19
	4-6	**0%**	157	1.79 (1.38)	1 (1–2)	0.36 (0.26)	0.25 (0.2–0.5)	0.32–0.40
		>0% to <25%	18	1.41 (0.87)	1 (1–2)	0.27 (0.18)	0.20 (0.17–0.4)	0.19–0.36
		25% to <75%	32	2.05 (1.16)	2 (1–2.5)	0.45 (0.26)	0.37 (0.25–0.51)	0.36–0.53
		≥ 75%	<5	NC	NC	NC	NC	NC

Abbreviations: FFS, Fee-for-Service; n, number of patients; NA, not applicable; NC, not calculated; PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists;

[a] *For subgroups with fewer than 5 patients, we did not calculate descriptive statistics*

Table D3. SABA Canister Equivalents Filled, by Age, Observation Interval Length, and PDC Subgroups

Subgroup category			Number of patients per subgroup (n)	Total SABA canister equivalents filled during observation range[a]		SABA canister equivalents filled *per observed month*[a]		
Age (years) as of index date	Range of observation interval lengths	Maintenance therapy PDC (%)		Mean (SD) per subgroup	Median per subgroup (25th–75th percentile)	Mean (SD) per subgroup	Median per subgroup (25th–75th percentile)	95% confidence interval of the mean per subgroup
	7-9	**0%**	183	2.80 (2.70)	2 (1–4)	0.35 (0.34)	0.22 (0.13–0.44)	0.30–0.40
		>0% to <25%	34	2.67 (3.22)	1.65 (1–3.1)	0.32 (0.36)	0.18 (0.13–0.38)	0.20–0.44
		25% to <75%	36	5.21 (3.97)	4 (2.3–7)	0.63 (0.46)	0.47 (0.29–0.88)	0.48–0.78
		≥ 75%	17	3.73 (0.72)	3 (2–5)	0.46 (0.31)	0.43 (0.25–0.63)	0.21–0.60
	10-11	**0%**	180	3.13 (2.92)	2 (1–4)	0.30 (0.27)	0.2 (0.1–0.4)	0.26–0.34
		>0% to <25%	27	3.61 (4.12)	2 (1–5)	0.34 (0.38)	0.18 (0.1–0.45)	0.20–0.49
		25% to <75%	36	5.09 (2.04)	5 (3–7)	0.48 (0.28)	0.45 (0.27–0.67)	0.38–0.57
		≥ 75%	14	6.08 (5.96)	3.1 (2–9)	0.58 (0.60)	0.29 (0.18–0.9)	0.27–0.90
	12	**0%**	145	6.06 (5.33)	4.8 (2–9)	0.51 (0.44)	0.40 (0.17–0.75)	0.43–0.58
		>0% to <25%	21	4.45 (4.01)	3 (1–8)	0.37 (0.33)	0.25 (0.08–0.67)	0.23–0.51
		25% to <75%	40	8.58 (5.48)	6.9 (5–12)	0.71 (0.46)	0.58 (0.42–1)	0.57–0.86
		≥ 75%	22	9.30 (7.20)	8.7 (3–11)	0.77 (0.60)	0.73 (0.25–0.92)	0.52–1.03

Abbreviations: FFS, Fee-for-Service; n, number of patients; NA, not applicable; NC, not calculated; PDC, proportion of days covered; SABA, short-acting beta$_2$ agonists;

[a] For subgroups with fewer than 5 patients, we did not calculate descriptive statistics