EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2021
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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## DuoResp Spiromax

International non-proprietary name: budesonide / formoterol

Procedure No. EMEA/H/C/002348/II/0033

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# Table of contents

**1. Background information on the procedure ..... 6**
1.1. Type II group of variations ..... 6
1.2. Steps taken for the assessment of the product ..... 7

**2. Scientific discussion ..... 7**
2.1. Introduction ..... 7
2.1.1. Problem statement ..... 7
2.1.2. About the product ..... 9
2.1.3. The development programme/compliance with CHMP guidance/scientific advice ..... 9
2.2. Non-clinical aspects ..... 10
2.2.1. Ecotoxicity/environmental risk assessment ..... 10
2.2.2. Conclusion of the non-clinical aspects ..... 10
2.3. Clinical aspects ..... 10
2.4. Clinical efficacy ..... 10
2.4.1. Discussion on clinical efficacy ..... 17
2.4.2. Conclusions on the clinical efficacy ..... 20
2.5. Clinical safety ..... 20
2.5.1. Discussion on clinical safety ..... 27
2.5.2. Conclusions on clinical safety ..... 28
2.5.3. PSUR cycle ..... 29
2.6. Risk management plan ..... 29
2.7. Update of the Product information ..... 29
2.7.1. User consultation ..... 30

**3. Benefit-Risk Balance ..... 30**
3.1. Conclusions ..... 30

**4. Recommendations ..... 30**

**5. EPAR changes ..... 31**

# List of abbreviations

| | |
|---|---|
| API | active pharmaceutical ingredient |
| AE | adverse event |
| APSD | aerodynamic particle size distribution |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| ATC | anatomical therapeutic chemical (classification system) |
| AUC0-inf | area under the plasma concentration time curve from time zero (pre-dose) to infinity |
| AUC0-t | area under the plasma concentration time curve from time zero (pre-dose) to the time of the last quantifiable concentration |
| AUClast | area under the plasma concentration time curve from time zero (pre-dose) to the last measurable concentration |
| bpm | beats per minute |
| BE | bioequivalence |
| BUD | budesonide |
| BF Spiromax | fixed-dose combination of budesonide and formoterol fumarate in the Spiromax Inhaler |
| COPD | chronic obstructive pulmonary disease |
| CSR | clinical study report |
| Cmax | maximum plasma concentration |
| CI | confidence interval |
| DBP | diastolic blood pressure |
| DPI | dry powder inhaler/multi-dose powder inhaler |
| ECG | electrocardiogram |
| FPD | fine particle dose |
| FDC | fixed-dose combination |
| FEV1 | forced expiratory volume in one second |
| FOR | formoterol fumarate |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GSD | geometric standard deviation |
| HPA | hypothalamic pituitary adrenocortical |
| HR | heart rate |

| | |
|---|---|
| ICS | inhaled corticosteroid |
| IP | inlet port |
| ITT | intent-to-treat population |
| LC | label claim |
| LS | least squares |
| LABA | long-acting β2 adrenergic agonist |
| LC-MS/MS | liquid chromatography-mass spectrometry/mass spectrometry |
| LLGR | lower leg growth rate |
| LLOQ | lower limit of quantification |
| MO | Major Objection |
| MMAD | mass median aerodynamic diameter |
| MedDRA | Medical dictionary for regulatory activities |
| MUC | modified urine cortisol |
| NGI | next generation impactor |
| OIP | orally inhaled product |
| PSD | particle size distribution |
| PIL/PL | patient information leaflet/package leaflet |
| PEF | peak expiratory flow |
| PIFR | peak inspiratory flow rate |
| PP | per protocol population |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PS | pre-separator |
| QTc | corrected QT interval |
| QTcB | corrected QT interval using the Bazzett correction formula |
| QTcF | corrected QT interval using the Fridericia correction formula |
| RMP | risk management plan |
| RMS | root mean square |
| SAE | serious adverse event |
| SmPC | summary of product characteristics |
| SBP | systolic blood pressure |
| T1/2 | terminal phase half-life |
| Tmax | time to maximum plasma concentration |

| | |
|---|---|
| TD | total dose |
| TEAR | treatment-emergent adverse events |
| UC | urine cortisol |
| WHO-DD | World Health Organisation-Drug Dictionary |
| µg | microgram |

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Teva Pharma B.V. submitted to the European Medicines Agency on 1 June 2020 an application for a group of variations.

The following variations were requested in the group:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.z | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | Type IB | I |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Type II variation – C.I.6.a. - Extension of Indication to include adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists; or in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists. The proposed extension to the indication is based upon data from the Literature. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly.
In addition, the MAH took the opportunity to make an administrative update to the Greek, Islandic, Irish and Maltese local representatives phone numbers in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.1. An updated RMP version 3.0 was submitted as part of the application.

Type IB variation - C.I.z other – updates of sections 4.2, 5.1 and 5.2 of the SmPC to update the information on paediatric data and section 4.4 of the SmPC to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as agreed during the assessment of the duplicate Budesonide/Formoterol Teva Pharma B.V. (EMEA/H/C/004882), which was approved in Jan 2020.

The group of variations requested amendments to the Summary of Product Characteristics (SmPC), Labelling and Package Leaflet (PL) and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Not applicable.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition

related to the proposed indication.

### *Scientific advice*

The MAH did not seek Scientific Advice at the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: Peter Kiely

| Timetable | Actual dates |
|---|---|
| Submission date | 1 June 2020 |
| Start of procedure: | 18 July 2020 |
| CHMP Rapporteur Assessment Report | 10 September 2020 |
| CHMP Co-Rapporteur Assessment Report | 11 September 2020 |
| PRAC Rapporteur Assessment Report | 17 September 2020 |
| PRAC Outcome | 1 October 2020 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 8 October 2020 |
| Request for supplementary information (RSI) | 15 October 2020 |
| MAH's responses submitted to the CHMP on | 18 February 2021 |
| Joint CHMP Rapporteur's preliminary Assessment Report circulated on | 23 March 2021 |
| PRAC Rapporteur Assessment Report | 26 March 2021 |
| Updated Joint CHMP Rapporteur's Assessment Report circulated on | 15 March 2021 |
| PRAC outcome | 09 April 2021 |
| Updated Joint CHMP Rapporteur's Assessment Report circulated on | 15 April 2021 |
| CHMP Opinion | 22 April 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

### *Disease or condition*

Asthma is an heterogenous disease characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms – wheeze, cough, dyspnoea, and chest tightness that may vary in time and in intensity together with variable expiratory airflow limitation. Asthma is a heterogenous disease with different underlying disease processes. Different cells play a role in the pathophysiology of this disease – lymphocytes, neutrophils, eosinophils, epithelial cells.

## *Therapeutic indication*

This application has been submitted to include the use in adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists; or in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists. The proposed extension to the indication was initially based upon data from the Literature.

## *Epidemiology*

Asthma is one of the most common major non-communicable diseases and for many, has a substantial impact on quality of life. Globally, asthma is ranked 16$^{th}$ among the leading causes of years lived with disability and 28$^{th}$ among the leading causes of burden of disease, as measured by disability-adjusted life years. Around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected. There is a large geographical variation in asthma prevalence, severity, and mortality. While asthma prevalence is higher in high income countries, most asthma-related mortality occurs in low-middle income countries.

## *Aetiology and pathogenesis*

The current evidence suggests that asthma is a complex multifactorial disorder and its etiology is increasingly attributed to interactions between genetic susceptibility, host factors, and environmental exposures. These include environmental factors (air pollution, pollens, mold and other aeroallergens, and weather), host factors (obesity, nutritional factors, infections, allergic sensitization), and genetic factors (asthma susceptibility loci on genes). Although underlying mechanisms of asthma are not yet fully understood, they may include airway inflammation, control of airway tone and reactivity. It is also now recognized that asthma may not be a single disease but a group of heterogeneous phenotypes with different aetiologies and prognoses.

## *Clinical presentation and diagnosis*

The clinical manifestations of asthma include recurrent episodes of wheezing, chest tightness, cough and shortness of breath. The symptoms are often worse at night or on waking from sleep. Usually, they resolve spontaneously or with the inhalation of a reliever medication. In other cases, they may worsen over hours or minutes, leading to more severe airflow obstruction and an 'attack' or exacerbation of asthma that is relieved only by extra medication. Some very severe episodes are life-threatening, although death from asthma in adulthood is uncommon and in most European countries mortality rates are falling.

Exacerbations of asthma are mostly provoked by respiratory infections – usually viral in origin – and are especially common in winter and shortly after the return of children to school after the summer holiday. In adults with allergic asthma (as indicated by the co-presence of rhinitis and conjunctivitis), symptoms are provoked by exposure to the relevant allergen(s), commonly those in-house dust or from pets, or encountered at work. Other common triggers include physical exertion (particularly in cold, dry air) and traffic pollution. Certain drugs such as β-adrenergic blockers and nonsteroidal anti-inflammatory agents can provoke asthma. A rare, but characteristic form of adult-onset asthma presents with nasal polyps and symptoms provoked by taking aspirin or similar nonsteroidal anti-inflammatory agents; however, its mechanism is unclear. Asthma exacerbations remain the main

reason for admission of people with asthma to hospital. While rates of hospital admission have gradually fallen in recent years, they remain high, particularly in the UK, Spain and Belgium.

### *Management*

There is currently no cure for most types of adult asthma, and the primary goals of management are to achieve and maintain control of symptoms; and to prevent asthma exacerbations. In many cases, it is also possible to improve and/or maintain respiratory function, to retain normal activity levels, to prevent the development of irreversible airway narrowing and to prevent deaths from asthma. Evidently, it is also desirable to avoid short- and long-term adverse events from asthma medication.

Pharmacological treatment comprises 'controller' medication (inhaled corticosteroids (ICS), with or without long-acting β2-agonists (LABA)) and 'reliever' medication taken as required to relieve symptoms (short-acting β2- agonists (SABA)). The amount of treatment is adjusted according to the severity and frequency of asthma symptoms. Patients' needs for treatment may change over time and treatment need to be adjusted accordingly. Mild asthma is usually controlled using SABA alone and on demand, or by the addition of low doses of ICS. Asthma of moderate severity can be controlled with a combination of low- or high-dose ICS with LABA. More severe asthma may necessitate the addition of other controller medications.

The most important long-term consequence of asthma is the development of persistent airway narrowing, which is non- or poorly responsive to treatment. It is unclear whether this is preventable by regular treatment with controller therapies. Death from asthma, although very uncommon in Europe, can occur in adults with all forms of the disease, especially if treatment has been suboptimal.

## 2.1.2. About the product

In the EU, DuoResp Spiromax is approved for the treatment of asthma and COPD in adult patients.

Asthma: DuoResp Spiromax is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: -in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists. or -in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

COPD: Symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Two strength are currently approved in the EU:

- DuoResp Spiromax 160 micrograms / 4.5 micrograms inhalation powder
- DuoResp Spiromax 320 micrograms/9 micrograms inhalation powder

## 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No CHMP scientific advice was requested by the MAH in relation to this variation.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00 corr 2), a justification for the absence of an environmental risk assessment (ERA) has been provided. The applicant states that the proposed budesonide/formoterol Spiromax 80/4.5, 160/4.5, 320/9 µg per dose, inhalation powder products would replace the currently marketed medicinal products and hence the exposure of the environment to budesonide and formoterol is not likely to increase. Therefore, the absence of ERA is considered acceptable.

### 2.2.2. Conclusion of the non-clinical aspects

No new non-clinical data have been submitted and the pre-clinical section 5.3 of the SmPC remains unchanged. This is considered acceptable by CHMP.

## *2.3. Clinical aspects*

No new clinical pharmacology studies were conducted to support this application, which was considered acceptable by the CHMP.

## *2.4. Clinical efficacy*

The MAH provided 10 literature references to support this variation application. In addition, the MAH discussed the results of a Phase 3b study (Study BFS-AS-306) to which 48 adolescents were enrolled upon request by CHMP. This study was a 12-week, multicenter, double-blind, double-dummy, randomized, controlled trial and the primary endpoint was the change from baseline in weekly average morning peak expiratory flow (AM PEF). It is presented below as a supportive study.

The following publications were provided:

| **Title of the study** | **The primary objective** | **Products/actives investigated** | **The number of adolescents/children enrolled** |
|---|---|---|---|
| (1) **Backer at al. 2019**<br><br>A multicenter, open-label, noninterventional study to evaluate the impact on clinical effects, user-friendliness and patients' acceptance of AirFluSal Forspiro in the treatment of asthma under real-life conditions (ASSURE) | The primary objective was to assess asthma control and any change in the quality of life in patients using an intuitive dry powder inhaler containing fluticasone propionate/salmeterol (AirFluSal Forspiro) for the treatment of asthma in everyday practice. | **fluticasone propionate/salmeterol AirFluSal Forspiro** | Not specified |
| (2) **Bender et al**<br><br>Comparative Analysis of Persistence to Treatment among Patients with Asthma or COPD Receiving AirFluSal Forspiro or Seretide Diskus Salmeterol/ Fluticasone Propionate Combination Therapy | The objective of this study was to compare persistence to salmeterol/fluticasone propionate combination treatment as AirFluSal Forspiro with persistence to Seretide Diskus in patients with asthma or COPD aged 12 years and above. | **fluticasone propionate/salmeterol**<br><br>AirFluSal Forspiro or Seretide Diskus | 310 |

| | | | |
|---|---|---|---|
| (3) The list of clinical trials from ClinicalTrials.gov | | | Unclear |
| (4) **Cates at al.**<br><br>Inhaled steroids with and without regular salmeterol for asthma: serious adverse events | The primary objective of this study was To assess risks of mortality and non-fatal serious adverse events (SAEs) in trials that randomised participants with chronic asthma to regular salmeterol and ICS versus the same dose of ICS. | Inhaled steroids with and without regular **salmetero**l | The data from 41 studies (27,951 participants) in adults and adolescents, along with eight studies (8453 participants) in children were analysed |
| (5) **Hantulik et al.**<br><br>Usage and usability of one dry powder inhaler compared to other inhalers at therapy start: an open, non-interventional observational study in Poland and Germany | The primary objective of this study was the validation of a questionnaire that can be used for assessing a successful inhalation technique, patient satisfaction as well as the compliance in daily practice. | **inhaler Easyhaler (EH) (Orion Pharma, Finland)**<br><br>active –unclear | 263 adult/adolescent patients with asthma and 164 children (≤ 12 years old) with asthmatic disease |
| (6) **Jogi et al.**<br><br>In Vitro Flow Rate Dependency of Delivered Dose and Fine Particle Dose of Salmeterol/Fluticasone Propionate Easyhaler and Seretide Diskus with Patient Flow Rates Collected in a Randomized Controlled Trial | | **fluticasone propionate/salmeterol**<br><br>S/F Easyhaler versus Seretide Diskus | Children<br><br>(n = 60)<br><br>Adolescents<br><br>and adults (n = 62) |
| (7) **Jorup et al.** Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma | | **Budesonide/formoterol**<br><br>**Symbicort MART (SMART) (AstraZeneca)** | 1847 adolescents |
| (8)**Kuna et al.** Randomized equivalence trial: A novel multidose dry powder inhaler and originator device in adult and adolescent asthma | To compare the efficacy and safety of FP-Sal delivered via a novel multidose dry powder inhaler (mDPI) versus an originator device in adolescent and adult patients with moderate-to-severe persistent asthma | **fluticasone propionate/salmeterol**<br><br>AirFluSal or Seretide Diskus | Unclear |
| (9) **Malmberg et al.** Evaluation of In Vitro and In Vivo Flow Rate Dependency of Budesonide/Formoterol Easyhaler | As a part of product optimization, a series of in vitro and in vivo studies on flow rate dependency were carried out. | **Budesonide/Formoterol Easyhaler** | 52 children (from 6 to 11 years) |
| (10) **Ole D. Wolthers**<br><br>Budesonide + formoterol fumarate dihydrate for the treatment of asthma | The aim of this paper was<br><br>to review the fixed dry powder combination of inhaled budesonide+formoterol fumarate dihydrate for<br><br>asthma treatment in adolescents and adults. | **Different Budesonide + formoterol fumarate dehydrate formulations.**<br><br>**It seems that in the majority of studies Symbicort Turbuhar was investigated** | unclear |

The most relevant publications submitted are summarised below:

**(7) Jorup et al. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma**

This was a post hoc analysis which assessed the efficacy and safety of budesonide/formoterol (BUD/FORM) maintenance and reliever therapy (MART) for treatment of persistent asthma in adolescent (age 12– 17 years) subgroups within six randomised, double-blind trials. The primary endpoint was time to first severe exacerbation. Secondary endpoints included number of severe exacerbations, asthma-related symptoms, night-time awakenings, morning peak expiratory flow,

forced expiratory volume in 1 s, as needed medication use and five-item asthma control questionnaire scores.

**Methods**

Studies eligible for inclusion were any randomised, double-blind trial comparing BUD/FORM MART with an active comparator in patients with persistent asthma, that were ⩾6 months in duration and which included patients aged 12–18 years. This individual patient-level analysis was conducted for Symbicort MART (SMART) by AstraZeneca to extend the licensed indication for the regimen to include patients aged ⩾12 years. As such, the data source for the analysis was the AstraZeneca clinical trials database, and included studies completed by November 2015.

Seven studies that met the criteria were identified in the AstraZeneca clinical trial database: SD-039–0667 (STEAM) [10], SD-039-0668 (STEP) [11], SD-039-0673 (STAY) [12], SD-039-0734 (SMILE) [13], SD-039-0735 (COMPASS) [14], NCT00242775 (AHEAD) [15] and NCT00839800 (SAKURA) [16]. Of these, six were included in the analysis: NCT00839800 was excluded since it randomised only 21 adolescents, all of whom were aged ⩾16 years. No additional studies were identified from the searches of the PubMed and Cochrane databases.

Each study included a 2-week run-in period, during which patients received either their usual ICS dose, BUD/FORM (Symbicort; AstraZeneca, Gothenburg, Sweden) 160/4.5 µg twice daily or BUD 200 µg·day-1 [10] as controller medication. Patients considered not well controlled on the run-in medication were then randomised to BUD/FORM MART or conventional fixed-dose maintenance therapy plus additional reliever therapy. The comparators, BUD (Pulmicort; AstraZeneca), FORM (Oxis; AstraZeneca) and terbutaline (Bricanyl; AstraZeneca) were administered via Turbohaler devices identical to those used for BUD/FORM; salmeterol/fluticasone (Seretide; GlaxoSmithKline, Brentford, UK) was administered via Evohaler or Diskus. Treatment duration was 6 months in three studies and 12 months in the remainder of the trials.

The primary efficacy endpoint for this analysis was time to first severe exacerbation, defined as the need for oral corticosteroid (OCS) for ⩾3 days and/or hospitalisation/emergency room care due to asthma worsening (online supplementary material). Time to first severe exacerbation was chosen since it was the primary endpoint in five of the six studies, one study recruited a population with relatively milder disease and hence included peak expiratory flow (PEF) as its primary endpoint.

Secondary efficacy endpoints included total number of severe exacerbations, changes in asthma-related symptoms, night-time awakenings, morning PEF, forced expiratory volume in 1 s (FEV1) at clinic visits, use of as-needed medication and five-item asthma control questionnaire (ACQ-5) scores (measured in three studies only [13–15]).

Statistical analyses were conducted on the adolescent (12–17 years) subgroup within each study.

Additional analyses were performed for the adult (⩾18 years) subgroups within each study, to assess whether the effect observed in adolescents was consistent with that in adults.

**Results**

1847 adolescents from six studies were randomised to BUD/FORM MART (n=694); BUD plus terbutaline (n=225); BUD/FORM plus terbutaline (n=441); BUD/FORM plus FORM (n=115); or salmeterol/ fluticasone plus terbutaline (n=372).

For the primary endpoint of time to first severe exacerbation, BUD/FORM MART was similar to or more effective than comparators in the adolescent population. Hazard ratios (HRs) numerically favoured BUD/FORM MART for all treatment comparisons in five of the six studies (ranging from 0.15 to 0.93)

and were similar for BUD/FORM MART and comparator (BUD/ FORM + FORM as needed) in the remaining study (HR 1.01).

In the pooled analysis, the risk of a severe exacerbation was found to be lower with BUD/FORM MART than comparator in the adolescent population (HR 0.49, 95% CI 0.34–0.70). However, there was statistically significant heterogeneity in the pooled estimate (likelihood ratio test, p=0.04).

For time to first severe exacerbation, the results observed for the adolescent population, both in the individual studies and in the pooled analysis, were consistent with those observed for the adult population.

In the adolescent subgroup, point estimates were in favour of BUD/FORM MART for secondary endpoints (total number of severe exacerbations, asthma symptom scores, night-time awakenings, as-needed inhalations, FEV1, morning PEF and ACQ-5 score) in five of the six studies versus comparators. In addition, pooled estimates were in favour of BUD/FORM MART for these secondary endpoints, although many of these analyses exhibited statistically significant heterogeneity. For these secondary efficacy endpoints, the results observed for the adolescent population, both in the individual studies and in the pooled analysis, were consistent with those observed for the adult population.

**(10) Ole D. Wolthers, Budesonide + formoterol fumarate dihydrate for the treatment of asthma**

**Methods**

The following databases were used in the literature search: PubMed, a service of the National Library of Medicine, New York, U.S.A, includes over 25 million citations for biomedical articles from the 1950s to 8 January 2016. For the review of efficacy primarily but not exclusively randomized double-blind trials were included.

All studies used a randomized, double-blind, parallel-group design. Where not indicated otherwise, a short-acting β-2 agonist was used for as-needed treatment. The outcomes were statistically significant except where marked by *.

Table 1: Summary of phase III efficacy studies of dry powder budesonide+formoterol fumarate dihydrate in bronchial asthma.

| Reference | N | Age(years) | Duration of Treatment (months) | Treatment | Primary outcomes |
|---|---|---|---|---|---|
| [23] Pauwels RA | 852 | ≥12 | 12 | bud 100 µg bid<br>bud+for 100 + 12 µg bid<br>bud 400 µg bid<br>bud+for 400 + 12 µg bid | <br>Exacerbation rate reduced<br><br>Exacerbation rate reduced |
| [29] Rabe KF | 697 | ≥11 | 6 | bud+for 80/4.5 µg qd+as<br>bud 160 µg qd | Exacerbation and hospitalization rates and use of oral steroids reduced |
| [30] Scicchitano R | 1890 | ≥11 | 12 | bud 160 µg bid<br>bud+for 320 + 9.5 µg od+as | <br>Time to first severe exacerbation increased; exacerbation, hospitalization rates and use of oral steroids reduced |
| [31] O´Byrne PM | 2760 | ≥4 | 12 | bud+for 80 + 4.5 µg bid<br>bud 320 µg bid<br>bud+for 80 + 4.5 µg bid+as | <br><br>Exacerbation rate reduced |
| [32] Rabe KF | 3394 | ≥12 | 12 | bud+for 160 + 4.5 µg bid nas<br>bud+for 160 + 4.5 µg bid<br>bud+for 160 + 4.5 µg bid + for as<br>bud+for 160 + 4.5 µg bid+as | <br><br><br>Time to first exacerbation reduced |
| [33] Kuna P | 3335 | ≥12 | 6 | bud+for 160 + 4.5 µg bid+as<br>flu+sal 250 + 50 µg bid<br>bud+for 320 + 9 µg bid | Time to first severe exacerbation increased; exacerbation rate and use of oral steroids reduced |
| [34] Bousquet J | 2309 | ≥12 | 6 | bud+for 320 + 9 µg bid+as<br>flu+sal 500 + 50 µg bid | Time to first severe exacerbation* |
| [35] Patel M | 303 | ≥16 | 5.5 | bud+for 400 + 12 µg bid+as | Exacerbation rate and use of oral steroids reduced |

od: once daily; bid.: twice daily; qd: four times daily; as: as needed; nas: no as-needed treatment; bud: budesonide; for: formoterol fumarate dihydrate; flu: fluticasone propionate sal: salmeterol xinafoate.

**Post-marketing surveillance studies**

The use of budesonide+formoterol fumarate dihydrate as maintenance and reliever therapy has been evaluated in more than 23 000 adolescent and adult patients as part of four real-world studies, which included open comparisons with fluticasone propionate+salmeterol xinofoate or conventional best practice. Budesonide+formoterol fumarate dihydrate was found to reduce the rate of exacerbations requiring hospital admissions or emergency room visits and the rate of exacerbations requiring oral corticosteroids as compared with fluticasone propionate+salmeterol xinofoate or conventional best practice. Patients treated with budesonide+formoterol fumarate dihydrate maintenance and reliever therapy received lower mean daily dose of corticosteroid compared with conventional best practice.

The use of oral corticosteroids was also lower than with fluticasone propionate+salmeterol xinofoate or conventional best practice.

**Unpublished studies**

The authors were able to identify 13 trials of budesonide+formoterol fumarate dihydrate maintenance and reliever therapy in 13,152 adolescent and adult asthma patients, of which only three were published. Only selected data from four studies were published and no data from six of the studies had been peer review published.

## *Supportive study*

The MAH conducted a Phase 3b study (Study BFS-AS-306), in patients 12 years and older with persistent asthma to demonstrate non-inferiority of BID BF SPIROMAX 160/4.5 mcg to BF TURBOHALER 200/6 mcg BID (Virchow et al 2016). This was a 12-week, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group study, and the primary endpoint was the change from baseline in weekly average AM PEF.

**Efficacy results in the overall population**

In both BF SPIROMAX and BF TURBOHALER treatment groups, there was an improvement in weekly average AM PEF over the 12-week treatment period and non-inferior efficacy was demonstrated for BF SPIROMAX versus BF TURBOHALER. No significant between-group differences were observed in the secondary efficacy endpoints of change from baseline in weekly average evening (PM) peak expiratory flow (PEF), the change from baseline in trough forced expiratory volume in 1 second (FEV1), the percentage of symptom-free days (24-hour period), and the percentage of rescue-free days (24-hour period).

**Efficacy results by age category**

Subjects in both treatment groups and all age categories showed improvement in all measures of efficacy.

*-Morning peak expiratory flow*

The change from baseline in AM PEF was specified as the primary efficacy endpoint in the study. The AM PEF values by treatment are shown for the total study population as well as for the age subgroups of adolescents aged 12 through 17 years, adults aged 18 through 64 years, and seniors aged 65 years and older (*Table 2*).

In the adolescent age subgroup, the mean change from baseline in the AM PEF was numerically greater in the BF SPIROMAX-treated patients than in those treated with BF TURBOHALER (37.9 L/min versus 23.4 L/min, respectively). Similarly, the mean change from baseline in the AM PEF was greater in the BF SPIROMAX-treated adolescents than in adult (18 through 64 years) or senior (≥65 years)

patients treated with BF SPIROMAX. Overall, the MAH was of the view that these data support the efficacy of BF SPIROMAX in adolescent patients with asthma.

Table 2: Mean Change from Baseline AM PEF at Endpoint by Treatment Group and Age Category (Per Protocol Population)

| Mean Change from Baseline in the Weekly Average AM PEF (L/min) | BF SPIROMAX 160/4.5 mcg AM PEF (n) | BF TURBOHALER 200/6 mcg AM PEF (n) |
|---|---|---|
| All ages | 24.1 (289) | 28.2 (284) |
| 12-17 years | 37.9 (17) | 23.4 (20) |
| 18-64 years | 23.4 (230) | 30.4 (225) |
| ≥65 years | 22.8 (42) | 18.3 (39) |

Source: Study BFS-AS-306 CSR Summary 15.2.1.1 and Summary 15.2.1.1.2.
AM=morning; BF=budesonide/formoterol; CSR=clinical summary report; n=number of patients; PEF=peak expiratory flow

*-Evening peak expiratory flow*

The PM PEF was a secondary efficacy endpoint for the study and the values by treatment are shown for the total study population as well as for the age subgroups of adolescents aged 12 through 17 years, adults aged 18 through 64 years, and seniors aged 65 years and older (*Table 3*). In all groups, the change from baseline in PM PEF for BF SPIROMAX-treated groups were similar or greater than the results for treatment with BF TURBOHALER. The increase from baseline PM PEF was greater in adolescent patients treated with BF SPIROMAX (34.4 L/min) than those treated with BF TURBOHALER (17.8 L/min). Although no formal comparison is possible due to the relatively small sample size, the results reasonably indicate that BF SPIROMAX 160/4.5 mcg is at least as effective as BF TURBOHALER 200/6 mcg in adolescent patients with asthma.

Table 3: Mean Change from Baseline PM PEF at Endpoint by Treatment Group and Age Category (Per Protocol Population)

| Mean Change from Baseline in the Weekly Average PM PEF (L/min) | BF SPIROMAX 160/4.5 mcg PM PEF (n) | BF TURBOHALER 200/6 mcg PM PEF (n) |
|---|---|---|
| All ages | 22.9 (289) | 26.9 (284) |
| 12-17 years | 34.4 (17) | 17.8 (20) |
| 18-64 years | 22.2 (230) | 29.2 (225) |
| ≥65 years | 22.4 (42) | 18.2 (39) |

Source: Study BFS-AS-306 CSR Summary 15.2.2.1 and Summary 15.2.2.1.2.
BF=budesonide/formoterol; CSR=clinical study report; n=number of patients; PEF=peak expiratory flow; PM=evening

*-Trough forced expiratory volume in 1 second*

The change from baseline trough (pre-dose) FEV1 values at the endpoint are shown by treatment for the total study population as well as for the age subgroups of adolescents aged 12 through 17 years, adults aged 18 through 64 years, and seniors aged 65 years and older (*Table 4*). In all groups, the trough FEV1 values for BF SPIROMAX and BF TURBOHALER were similar, with a change from baseline value for adolescent patients of 0.7 L versus 0.8 L for BF SPIROMAX and BF TURBOHALER treatments, respectively.

Table 4*:* Mean Change from Baseline Trough FEV1 at Endpoint by Treatment Group and Age Category (Per Protocol Population)

| Mean Change from Baseline Trough $FEV_1$ (L) | BF SPIROMAX 160/4.5 mcg $FEV_1$ (n) | BF TURBOHALER 200/6 mcg $FEV_1$ (n) |
|---|---|---|
| All ages | 0.3 (283) | 0.3 (280) |
| 12-17 years | 0.7 (16) | 0.8 (20) |
| 18-64 years | 0.3 (225) | 0.3 (223) |
| ≥65 years | 0.2 (42) | 0.2 (37) |

Source: Study BFS-AS-306 CSR Summary 15.2.5.1 and Summary 15.2.5.1.2.
BF=budesonide/formoterol; CSR=clinical study report; $FEV_1$=forced expiratory flow in 1 second; n=number of patients

*-Rescue-free days*

Rescue medication use was recorded on a daily basis by patients in a paper diary. The use was recorded during the run-in period to establish a study baseline and throughout the treatment period.

The change from baseline in the percentage of rescue-free days at week 12 is shown by treatment for the total study population as well as for the age subgroups of adolescents aged 12 through 17 years, adults aged 18 through 64 years, and seniors aged 65 years and older (*Table 5*). In all groups, the increased percentage of rescue-free days for BF SPIROMAX and BF TURBOHALER were similar over 12 weeks, with a change from baseline for adolescent patients of 35.8% versus 32.0% for BF SPIROMAX and BF TURBOHALER treatments, respectively.

Table 5*:* Mean Change from Baseline in the Percentage of Rescue-Free Days (24-Hour Period) at Week 12 by Treatment Group and Age Category (Per Protocol Population)

| Mean Change from Baseline in Percentage of Rescue-Free Days (24-Hour Period) at Week 12 (%) | BF SPIROMAX 160/4.5 mcg Rescue-Free Days (n) | BF TURBOHALER 200/6 mcg Rescue-Free Days (n) |
|---|---|---|
| All ages | 37.8 (290) | 40.2 (284) |
| 12-17 years | 35.8 (17) | 32.0 (20) |
| 18-64 years | 38.2 (231) | 42.4 (225) |
| ≥65 years | 36.4 (42) | 31.8 (39) |

Source: Study BFS-AS-306 CSR Summary 15.2.4.1 and Summary 15.2.4.1.2.
BF=budesonide/formoterol; CSR=clinical study report; n=number of patients

*-Symptom-free days*

Symptoms of cough, wheeze, shortness of breath, and chest tightness were assessed by patients each AM and PM before determining PEF and administration of study drug or rescue medication. Daytime and nighttime symptoms were recorded on a daily basis using a 5-point (daytime) or 4-point (nighttime) scoring system with 0 representing no symptoms. A 24-hour symptom-free period was defined as an asthma symptom score of 0 for both AM and PM assessments.

The change from baseline in the percentage of symptom-free days at week 12 are shown by treatment for the total study population as well as for the age subgroups of adolescents aged 12 through 17 years, adults aged 18 through 64 years, and seniors aged 65 years and older (*Table 6*).

In all groups, the increased percentage of symptom-free days for BF SPIROMAX and BF TURBOHALER were similar over 12 weeks, with a change from baseline for adolescent patients of 45.3% versus 39.4% for BF SPIROMAX and BF TURBOHALER treatments, respectively.

Table 6*:* Mean Change from Baseline in the Percentage of Symptom-Free Days (24-Hour Period) at Week 12 by Treatment Group and Age Category (Per Protocol Population)

| Change from Baseline in Percentage of Symptom-Free Days (24-Hour Period) at Week 12 (%) | BF SPIROMAX 160/4.5 mcg Symptom-Free Days (n) | BF TURBOHALER 200/6 mcg Symptom-Free Days (n) |
|---|---|---|
| All ages | 30.0 (290) | 32.5 (284) |
| 12-17 years | 45.3 (17) | 39.4 (20) |
| 18-64 years | 28.0 (231) | 32.0 (225) |
| ≥65 years | 34.7 (42) | 31.5 (39) |

Source: Study BFS-AS-306 CSR Summary 15.2.3.1 and Summary 15.2.3.1.2.
BF=budesonide/formoterol; CSR=clinical study report; n=number of patients

**Summary of clinical efficacy results**

In each age subgroup, the size of the treatment effect was similar for BF SPIROMAX and BF TURBOHALER. While the sample size of the adolescent population does not allow for a formal statistical comparison, the numeric differences between both the response in adolescents to BF SPIROMAX and BF TURBOHALER, and the response of the different age subgroups to BF SPIROMAX, together provide strong support for the efficacy of BF SPIROMAX in adolescent patients with asthma.

## 2.4.1. Discussion on clinical efficacy

The MAH submitted this application to extend the indication in Asthma to adolescents (aged 12-17 years).

The MAH initially provided 10 literature references to support this extension of indication. Nevertheless, upon request by CHMP, the MAH provided further justification regarding the use of DuoResp Spiromax in adolescents as well as all available data for the use of DuoResp Spiromax in Adolescents patients.

*Literature references*

Only three out of the ten publications submitted as part of this application where considered to be relevant by CHMP.

-Cates at al. Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Please see section on clinical safety.

- Ole D. Wolthers, Budesonide + formoterol fumarate dihydrate for the treatment of asthma

Upon request by CHMP, the MAH provided further clarification on the types of budenoside/formoterol formulations investigated in published studies and if in any study DuoResp/BiResp Spiromax was used. It was highlighted that the publication by Wolthers (2016) reviewed studies of the BF combination that included adolescent patients with asthma. However, neither the Wolthers study nor the original references cited provided data by age subgroups. In some cases, the data for children (ages 4 through 11 years) were reported separately, but the data for adolescent patients (ages 12 through 17 years) were reported in combination with adults (O'Byrne et al 2005). Additionally, it was clarified that none of the studies in the review by Wolthers included treatment with the BF SPIROMAX inhaler. While Wolthers did not report on age subgroups, a post-hoc analysis by Jorup et al (2018) included several of the studies cited by Wolthers and compared efficacy and safety of the BF combination in adolescent

and adult patients with asthma. The results of this post-hoc analysis, which included 1847 adolescent patients (12 through 17 years) with asthma from 6 clinical studies is discussed below.

- Jorup et al. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma

This study focused on the maintenance and reliever therapy of the budesonide/formoterol combination. In this publication, the efficacy and safety of Symbicort MART (SMART) investigated in six randomised, double-blind trials adolescents (age 12– 17 years) with persistent asthma were presented.

Upon request by CHMP, an additional discussion was provided by the MAH in relation to the use of other budenoside/formoterol formulations in adolescents. The response of adolescent patients with asthma has been compared to adult patients with respect to the efficacy and safety of the budesonide/ formoterol combination used as both maintenance and reliever therapy (MART). A post-hoc analysis of patient data from 6 studies (n=1847 adolescents) demonstrated little difference in response between adult and adolescent patients across numerous efficacy endpoints, encompassing both lung function and symptomatic improvement as well as in reducing the risk of severe exacerbation.

The analysis assessed the efficacy and safety of BF MART for treatment of persistent asthma in adolescent (age 12 through 17 years) subgroups within 6 randomised, double-blind trials. The authors concluded that their analysis supported the use of the BF combination as MART in adolescents with persistent asthma and that BF efficacy and safety in adolescent patients were consistent with the BF efficacy and safety reported for adults.

Furthermore, the authors conducted a literature search for publications reporting on studies in the Symbicort Turbohaler clinical research program that included patients who were 12 to 17 years of age. A total of 7 studies that had been completed by November 2015 were found. One of these was excluded since it randomised only 21 adolescents, all of whom were ≥16 years of age.

The primary endpoint in all studies was time to first severe exacerbation of asthma symptoms. Secondary endpoints included number of severe exacerbations, asthma-related symptoms, night-time awakenings, AM PEF, FEV1, as-needed medication use, and 5-item asthma control questionnaire scores.

In adolescent patients (n=1847), efficacy of BF MART was similar to or greater than that of comparators across each of the studies in reducing the risk of a first severe exacerbation. This was consistent with outcomes in the adult subgroups (n=12197), both in the individual studies and in the pooled analysis. Similar treatment benefits for BF MART were observed for secondary endpoints. As-needed medication use was lower with BF MART than comparators, and BF as-needed use was lower in adolescents than adults. The safety profile of BF MART observed in the adolescent subgroups was similar to that reported in all patients. No signals for systemic adverse events or new safety concerns were identified in the adolescent population. See discussion on clinical safety.

The MAH also highlighted that there is precedent for approval of the budesonide/formoterol combination for use in adolescents based on clinical data obtained in adults i.e. the combinations of Airbufo Forspiro and Bufomix Easyhaler were both approved for use in adults and adolescents with asthma based on the demonstration of bioequivalence in healthy adults (Sandoz PAR 2018, Orion PAR 2014). Thus, the MAH considered that the orally inhaled combination can be used safely in adolescents based on extrapolation of clinical data in adults to adolescents.

In general, CHMP agreed that this analysis can support the use of BUD/FORM MART (Symbicort MART) in adolescents with persistent asthma. Of note, BiResp/Duoresp Spiromax was not investigated in any of these studies.

*Study BFS-AS-306*

Following the initial approval in adults based on bioequivalence studies, a non-inferiority study (BFS-AS-306) was conducted which compared the efficacy and safety of BF SPIROMAX (DuoResp Spiromax,160/4.5 mcg twice daily [BID]) and BF TURBOHALER, the reference medicinal product (Symbicort Turbohaler, 200/6 mcg BID) over 12 weeks in both adult and adolescent patients with asthma. The efficacy results for adolescents and adults are discussed below. This was a 12-week, multicenter, double-blind, double-dummy, randomized, controlled Phase 3b study in which 48 adolescents were enrolled. The primary endpoint was the change from baseline in weekly average morning peak expiratory flow (AM PEF).

The primary endpoint of this study was met and non-inferior efficacy was considered to be demonstrated for BF SPIROMAX versus BF TURBOHALER by the MAH. While the sample size of the adolescent population did not allow for a formal statistical comparison, the available efficacy data indicated that BF SPIROMAX was efficacious in Adolescents patients. Although for establishing equivalence or non-inferiority, two endpoints (FEV1 or PEF) should be measured i.e. after 12 hour (to assess the LABA component) and 24 hour (to assess the ICS component) of withdrawal of the ICS/LABA inhaler; CHMP considered these efficacy results as supportive data for this extension of indication to adolescents despite the study limitations (choice of endpoints and low numbers of adolescents included).

*Extrapolation*

In adults and adolescents with asthma, the relationship between the inspiratory flow rates achievable with the SPIROMAX and the TURBOHALER devices were found to be equivalent for adults and adolescents. According to the MAH, the fact that the inspiratory flow rates achieved by adolescents with SPIROMAX compared to TURBOHALER are equivalent to the same comparison for adult inspiratory flow rates supports that equivalence of BF SPIROMAX and BF TURBOHALER demonstrated in adults could reasonably be extrapolated to adolescents.

It was also highlighted that the approval for use in adolescents based on adult data is consistent with the many therapeutic similarities in the use of ICS/LABA combinations in adult and adolescent patients. While in some cases a lower dose of an ICS/LABA combination has been developed for paediatric patients, the development of lower doses has not been required for the adolescent population. Accordingly, there is no dose adjustment in the BF combinations used to treat adults versus adolescent patients with asthma. The therapeutic similarity between adult and adolescent patients with asthma is also reflected in the Global Initiative for Asthma (GINA) recommendations (GINA 2020). While the therapeutic recommendations for children aged 6 through 11 years are distinct, the therapeutic recommendations for adolescent patients are the same as those for adult patients.

Overall, CHMP considered that the respective requirements for the availability of paediatric data defined in the orally inhaled products (OIPs) guideline (CHMP/EWP/4151/00 Rev. 1) are no longer interpreted as narrowly as in 2014 when the medicinal product was first approved. Furthermore, CHMP acknowledged that there are now several precedents in decentralised procedures where a lower age limit of 12 years has been granted, and provided that the reference product included an adolescent indication and that therapeutic equivalence in adults was demonstrated for the reference medicinal product. Moreover, in both pharmacokinetic / bioequivalence studies in adults (BFS-BE-108 and BFS-BE-109) exposure to the active moieties included in DuoResp Spiromax (middle strength: 160/4.5; high strength: 320/9) was shown to be equivalent to the respective presentations of the reference medicinal product (Symbicort Turbohaler), both in the presence and absence of charcoal block. Therefore, CHMP agreed with the MAH's position i.e. that the benefit/risk obtained in adults based on PK studies in healthy volunteers can be extrapolated to adolescents in asthma, taking into consideration that the lungs of adults and adolescents are sufficiently comparable.

As part of this application, the MAH also submitted a type IB variation to remove the warning regarding the risk of growth retardation in children and the guidance on how to address this risk as the product was initially authorised in Adults only. Nevertheless, as the extension of indication to Adolescents is considered to be approvable by CHMP, it was deemed necessary to retain the above-

mentioned warning in DuoResp Spiromax PI. Thus, the changes proposed as part of this type IB variation were withdrawn by the MAH.

### 2.4.2. Conclusions on the clinical efficacy

The final indication granted by CHMP is as follows:

*DuoResp Spiromax is indicated in adults **and adolescents (12 years and older) for** the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting $\beta_2$ adrenoceptor agonist) is appropriate:*

*-in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting $\beta_2$ adrenoceptor agonists.*
*or*
*-in patients already adequately controlled on both inhaled corticosteroids and long-acting $\beta_2$ adrenoceptor agonists.*

## *2.5. Clinical safety*

### *Introduction*

The MAH provided 10 literature references to support this variation application. Only relevant Lit Ref are presented/discussed below.

**(4) Cates at al. Inhaled steroids with and without regular salmeterol for asthma: serious adverse events**

The primary objective of this study was to assess risks of mortality and non-fatal serious adverse events (SAEs) in trials that randomised participants with chronic asthma to regular salmeterol and ICS versus the same dose of ICS. Randomised trials were identified using the Cochrane Airways Group Specialised Register of trials. The date of the most recent search was 10 October 2018.

Parallel-design randomised trials involving adults, children, or both with asthma of any severity who were randomised to treatment with regular salmeterol and ICS (in separate or combined inhalers) versus the same dose of ICS of at least 12 weeks in duration were included.

The data from 41 studies (27,951 participants) in adults and adolescents, along with eight studies (8453 participants) in children were analysed. All except 542 adults (and none of the children) were given salmeterol and fluticasone in the same (combination) inhaler.

**Deaths**

Eleven of a total of 14,233 adults taking regular salmeterol and ICS died, as did 13 of 13,718 taking regular ICS at the same dose. The pooled Peto odds ratio (OR) was 0.80 (95% confidence interval (CI) 0.36 to 1.78; participants = 27,951; studies = 41; IQ = 0%; moderate-certainty evidence), i.e. for every 1000 adults treated for 25 weeks, one death occurred among those on ICS alone, and the corresponding risk among those taking salmeterol and ICS was also one death (95% CI 0 to 2 deaths).

No children died, and no adults or children died of asthma, therefore the mortality in children and the asthma mortality in any age group remain uncertain.

***Non-fatal serious adverse events***

A total of 332 adults receiving regular salmeterol with ICS experienced a non-fatal SAE of any cause, compared to 282 adults receiving regular ICS. The pooled Peto OR was 1.14 (95% CI 0.97 to 1.33;

participants = 27,951; studies = 41; IQ = 0%; moderate-certainty evidence). For every 1000 adults treated for 25 weeks, 21 adults on ICS alone had an SAE, and the corresponding risk for those on salmeterol and ICS was 23 adults (95% CI 20 to 27).

Sixty-five of 4229 children given regular salmeterol with ICS suffered an SAE of any cause, compared to 62 of 4224 children given regular ICS. The pooled Peto OR was 1.04 (95% CI 0.73 to 1.48; participants = 8453; studies = 8; IQ = 0%; moderate-certainty evidence). For every 1000 children treated for 23 weeks, 15 children on ICS alone had an SAE, and the corresponding risk for those on salmeterol and ICS was 15 children (95% CI 11 to 22).

***Asthma-related serious adverse events***

Eighty and 67 adults in each group, respectively, experienced an asthma-related non-fatal SAE. The pooled Peto OR was 1.15 (95% CI 0.83 to 1.59; participants = 27,951; studies = 41; IQ = 0%; low-certainty evidence). For every 1000 adults treated for 25 weeks, five receiving ICS alone had an asthma-related SAE, and the corresponding risk among those on salmeterol and ICS was six adults (95% CI 4 to 8).

Twenty-nine children taking salmeterol and ICS and 23 children taking ICS alone reported asthma-related events. The pooled Peto OR was 1.25 (95% CI 0.72 to 2.16; participants = 8453; studies = 8; IQ = 0%; moderate-certainty evidence). For every 1000 children treated for 23 weeks, five receiving an ICS alone had an asthma-related SAE, and the corresponding risk among those receiving salmeterol and ICS was seven children (95% CI 4 to 12).

**Authors' conclusions**

The risk of death or serious adverse events in either adults or children was no different. However, trial authors reported no asthma deaths among 27,951 adults or 8453 children randomised to regular salmeterol and ICS or ICS alone over an average of six months.

Therefore, the risk of dying from asthma on either treatment was very low, but we remain uncertain about whether the risk of dying from asthma is altered by adding salmeterol to ICS.

Base on this data it can be estimated that at least 152 adults and 139 children must be treated with combination salmeterol and ICS for six months for one additional person to be admitted to the hospital (compared to treatment with ICS alone). These possible risks still have to be weighed against the

benefits experienced by people who take combination treatment.

**(7) Jorup et al. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma**

**Safety**

The incidence of adverse events and the types of adverse events reported were similar for adolescents receiving BUD/FORM MART and those receiving comparator treatments.

The proportion of adolescents experiencing a serious adverse event or discontinuing due to an adverse event was very low and similar between treatment comparisons.

All treatments were well tolerated and there were no adverse events with fatal outcomes reported among adolescents using BUD/FORM MART or comparators.

**(10) Ole D. Wolthers, Budesonide + formoterol fumarate dihydrate for the treatment of asthma**

**Safety and tolerability**

Conventionally, systemic activity of inhaled corticosteroids in adults has been assessed by urine cortisol measures of hypothalamic-pituitary-adrenal-function. Extensive evaluations have not indicated that inhaled budesonide in recommended doses in adults with asthma may cause clinically significant hypothalamic-pituitary-adrenal insufficiency and there are no data to suggest that this may be different with the fixed combination of budesonide-formoterol fumarate dihydrate. If sensitive repetitive serum measures of basal adrenal activity are used, however, dose-related suppressive effects with specific application systems may be detected. Such evaluations of the fixed combination of budesonide-formoterol fumarate dehydrate appear not to have been reported.

Hypokalemia, hyperglycemia, and tachycardia are possible systemic effects of LABAs. Mortality and asthma-related serious adverse events, overall and cardiac serious adverse events, and discontinuations due to adverse events were assessed in six double-blind, randomized clinical trials in 14,346 adolescents and adults with asthma during dry powder budesonide+formoterol fumarate dihydrate maintenance and reliever therapy for at least 6 months. The pooled data from the six trials showed that budesonide+formoterol fumarate dihydrate was well tolerated and was not found to be associated with an increased risk of death or cardiac-related serious adverse events or discontinuations due to adverse events.

A recent analysis with additional data supported the observations. The tolerability profile of the fixed combination of budesonide+formoterol fumarate dihydrate appears to correspond with its individual components, the treatment being generally well tolerated with ≤10% of patients experiencing treatment-related adverse effects. Oropharyngeal candidiasis, dysphonia, tremor, palpitations, and pneumonia were the most frequent complaints. Tolerability profiles would be expected not to differ between the commercially available dry powder combinations of budesonide+formoterol fumarate dihydrate. There are no tolerability profile head-to-head comparisons with other fixed combinations. Finally, a randomized, double-blind, double-dummy, crossover, placebo- controlled study assessed the acute tolerability of budesonide+ formoterol fumarate dihydrate in 14 patients with asthma in whom two inhalations of 160/4.5 µg twice daily and 10 additional doses adding up to a total daily dose of 1920 + 54 µg; or formoterol fumarate dihydrate 54 µg/day; or placebo on three separate study days. Statistically significant changes in serum potassium, pulse rate, blood pressure, QTinterval, blood glucose, and plasma lactate occurring with budesonide+formoterol fumarate dihydrate treatment were considered clinically unimportant. The authors concluded that the fixed combination of budesonide+formoterol fumarate dihydrate was well tolerated at high doses such as might be used by patients using the combination inhaler for relief of symptoms of asthma.

In addition, upon request by CHMP, the MAH discussed the results of a Phase 3b study (Study BFS-AS-306) to which 48 adolescents were enrolled.

## *Study BFS-AS-306*

Study BFS-AS-306 assessed safety by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, physical examination findings, oropharyngeal examination findings, and concomitant medication usage.

## *Patient exposure*

A total of 303 patients in the BF SPIROMAX treatment group received at least 1 dose of study drug and were included in the safety population. A total of 117 of those patients (39%) reported at least 1 adverse event; 14 patients (5%) had treatment-related adverse events, 1 patient (<1%) had a serious adverse event, and 2 patients (<1%) withdrew due to adverse events. No patient died during the study (Table 6).

## *Adverse events*

*Overview of Adverse Events by Treatment Group and Age*

The proportion of patients reporting adverse events and treatment-related adverse events was similar or lower for adolescent patients in the BF SPIROMAX treatment group when compared either to adolescent patients who received BF TURBOHALER, or to the adult (18 through 64 years) and senior (≥ 65 years) patients treated with BF SPIROMAX (*Table 7*).

*Adverse Events Occurring in at Least 2% of the Population by Treatment Group and Age Category*

The distribution of frequently reported adverse events (occurring in 2% or more of patients in the BF SPIROMAX treatment group) varied somewhat among age categories but incidence was low for all system organ classes (SOCs) and preferred terms (PTs) (*Table 8*).

The number (%) of frequently reported adverse events (≥2%) in adolescent patients treated with BF SPIROMAX was low (3 [17%]) when compared to both adolescent patients treated with BF TURBOHALER (11 [55%]), or to adults 18 through 64 years (96 [40%]) or seniors 65 years and older (18 [42%]) treated with BF SPIROMAX (*Table 8*).

Table 7*:* Overview of Adverse Events by Treatment Group and Age Category (Safety Population)

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | | All Study Population | |
|---|---|---|---|---|---|---|---|---|
| **Adverse Events n (%)** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** |
| | N=18 | N=20 | N=242 | N=239 | N=43 | N=40 | N=303 | N=299 |
| Any adverse event | 3 (17) | 11 (55) | 96 (40) | 78 (33) | 18 (42) | 17 (43) | 117 (39) | 106 (35) |
| Treatment-related adverse events | 1 (6) | 0 | 10 (4) | 5 (2) | 3 (7) | 0 | 14 (5) | 5 (2) |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Serious adverse events | 0 | 0 | 1 (<1) | 2 (<1) | 0 | 1 (3) | 1 (<1) | 3 (1) |
| Withdrawals due to adverse events | 0 | 0 | 1 <1) | 0 | 1 (2) | 2 (5) | 2 (<1) | 2 (<1) |

Source: EMEA Response Summary 1 and Study BFS-AS-306 CSR Table 9.
BF=budesonide/formoterol; EMEA=European Medicines Agency; n=number of patients with adverse event; N=number of patients in treatment group

Table 8*:* Adverse Events Occurring in at Least 2% of the Population by System Organ Class, Preferred Term, Treatment Group, and Age Category (Safety Population)

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | |
|---|---|---|---|---|---|---|
| **System Organ Class MeDDRA 16.0 Preferred Term, n (%)** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** |
| | **N=18** | **N=20** | **N=242** | **N=239** | **N=43** | **N=40** |
| **Patients with at least 1 adverse event** | **3 (17)** | **11 (55)** | **96 (40)** | **78 (33)** | **18 (42)** | **17 (43)** |
| Cardiac disorders | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Angina pectoris | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Bradycardia | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Eye disorders | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Cataract | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Conjunctivitis | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Gastrointestinal disorders | 0 | 1 (5) | 14 (6) | 11 (5) | 4 (9) | 2 (5) |
| Abdominal pain | 0 | 1 (5) | 0 | 0 | 1 (2) | 1 (3) |
| Diarrhoea | 0 | 0 | 5 (2) | 2 (<1) | 0 | 0 |
| Abdominal pain upper | 0 | 0 | 4 (2) | 1 (<1) | 0 | 0 |
| Gastritis | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Nausea | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Aphthous stomatitis | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| General disorders and administration site conditions | 0 | 0 | 8 (3) | 4 (2) | 1 (2) | 0 |
| Pyrexia | 0 | 0 | 5 (2) | 2 (<1) | 1 (2) | 0 |

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | |
|---|---|---|---|---|---|---|
| **System Organ Class MeDDRA 16.0 Preferred Term, n (%)** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** |
| Infections and Infestations | 2 (11) | 9 (45) | 53 (22) | 53 (22) | 6 (14) | 7 (18) |
| Nasopharyngitis | 1 (6) | 4 (20) | 28 (12) | 18 (8) | 2 (5) | 3 (8) |
| Pharyngitis | 0 | 1 (5) | 4 (2) | 3 (1) | 0 | 0 |
| Tonsillitis | 0 | 1 (5) | 0 | 0 | 0 | 0 |
| Sinusitis | 0 | 2 (10) | 0 | 0 | 0 | 1 (3) |
| Viral infection | 1 (6) | 0 | 0 | 0 | 0 | 0 |
| Viral pharyngitis | 0 | 1 (5) | 0 | 0 | 0 | 0 |
| Viral rhinitis | 0 | 1 (5) | 0 | 0 | 0 | 0 |
| Rhinitis | 0 | 0 | 6 (2) | 6 (3) | 0 | 1 (3) |
| Bronchitis | 0 | 0 | 3 (1) | 6 (3) | 0 | 1 (3) |
| Influenza | 0 | 0 | 2 (<1) | 6 (3) | 0 | 0 |
| Upper respiratory tract infection | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Laryngitis | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Folliculitis | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Oral herpes | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Respiratory tract infection bacterial | 0 | 0 | 0 | 0 | 1 (2) | 0 |

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | |
|---|---|---|---|---|---|---|
| System Organ Class MeDDRA 16.0 Preferred Term, n (%) | BF SPIROMAX 160/4.5 mcg | BF TURBOHALER 200/6 mcg | BF SPIROMAX 160/4.5 mcg | BF TURBOHALER 200/6 mcg | BF SPIROMAX 160/4.5 mcg | BF TURBOHALER 200/6 mcg |
| Musculoskeletal and connective tissue disorders | 0 | 0 | 15 (6) | 3 (1) | 0 | 3 (8) |
| Back pain | 0 | 0 | 4 (2) | 1 (<1) | 0 | 0 |
| Muscle spasms | 0 | 0 | 0 | 0 | 0 | 2 (5) |
| Musculoskeletal stiffness | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Myalgia | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Nervous system disorders | 0 | 2 (10) | 16 (7) | 20 (8) | 5 (12) | 4 (10) |
| Headache | 0 | 2 (10) | 14 (6) | 19 (8) | 4 (9) | 3 (8) |
| Dizziness | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Aphonia | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Hyposmia | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Respiratory, thoracic, and mediastinal disorders | 1 (6) | 1 (5) | 29 (12) | 15 (6) | 3 (7) | 6 (15) |
| Cough | 1 (6) | 1 (5) | 9 (4) | 6 (3) | 1 (2) | 1 (3) |
| Oropharyngeal pain | 0 | 0 | 7 (3) | 3 (1) | 0 | 2 (5) |
| Dysphonia | 0 | 0 | 7 (3) | 1 (<1) | 2 (5) | 0 |
| Dyspnoea | 0 | 0 | 4 (2) | 1 (<1) | 0 | 3 (8) |
| Epistaxis | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Pulmonary congestion | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Rhonchi | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Skin and subcutaneous tissue disorders | 0 | 1 (5) | 0 | 0 | 1 (2) | 1 (3) |
| Rash | 0 | 1 (5) | 0 | 0 | 0 | 0 |
| Eczema | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Skin lesion | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Injury, poisoning and procedural complications | 0 | 0 | 0 | 0 | 2 (5) | 0 |
| Contusion | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Fall | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Psychiatric disorders | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Sleep disorder | 0 | 0 | 0 | 0 | 0 | 1 (3) |
| Vascular disorders | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |
| Hypertension | 0 | 0 | 0 | 0 | 1 (2) | 1 (3) |

Source: EMEA Response Summary 2

BF=budesonide/formoterol; EMEA=European Medicines Agency; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with adverse event; N=number of patients in treatment group; PT=preferred term; SOC=system organ class

Note: Patients are counted only once in each preferred term category, and only once in each SOC category.

*Treatment-Related Adverse Events by Treatment Group and Age Category*

In all the age subgroups, the proportion of patients reporting treatment-related adverse events was low (*Table 9*). The proportion was similar for patients in the BF SPIROMAX treatment group in all 3 age categories (*Table 9*). The only treatment-related adverse events reported in the adolescent age subgroup was cough in 1 patient (6%) which is a commonly reported adverse reaction associated with budesonide or formoterol (SYMBICORT TURBOHALER SmPC).

Table 9*:* Treatment-Related Adverse Events by System Organ Class, Preferred Term, Treatment Group, and Age Category (Safety Population)

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | |
|---|---|---|---|---|---|---|
| **System Organ Class MedDRA 16.0 Preferred Term, n (%)** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** |
| | **N=18** | **N=20** | **N=242** | **N=239** | **N=43** | **N=40** |
| **Patients with at least 1 treatment-related adverse events** | **1 (6)** | **0** | **10 (4)** | **5 (2)** | **3 (7)** | **0** |
| Gastrointestinal disorders | 0 | 0 | 2 (<1) | 2 (<1) | 1 (2) | 0 |
| Abdominal pain upper | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Aphthous stomatitis | 0 | 0 | 0 | 0 | 1 (2) | 0 |
| Dry mouth | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Stomatitis | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Tongue discolouration | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Infections and Infestations | 0 | 0 | 3 (1) | 1 (<1) | 0 | 0 |
| Candidiasis | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Nasopharyngitis | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Oral candidiasis | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Respiratory tract infection | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Tonsillitis | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Nervous system disorders | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Headache | 0 | 0 | 1 (<1) | 0 | 0 | 0 |

| | Ages 12-17 years | | Ages 18-64 years | | Ages ≥65 years | |
|---|---|---|---|---|---|---|
| **System organ class MedDRA 16.0 preferred term, n (%)** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** | **BF SPIROMAX 160/4.5 mcg** | **BF TURBOHALER 200/6 mcg** |
| Respiratory, thoracic, and mediastinal disorders | 1 (6) | 0 | 5 (2) | 2 (<1) | 2 (5) | 0 |
| Dysphonia | 0 | 0 | 3 (1) | 1 (<1) | 2 (5) | 0 |
| Cough | 1 (6) | 0 | 1 (<1) | 0 | 0 | 0 |
| Dry throat | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Rhinorrhoea | 0 | 0 | 1 (<1) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | 0 | 0 | 0 | 1 (<1) | 0 | 0 |
| Eczema | 0 | 0 | 0 | 1 (<1) | 0 | 0 |

Source: EMEA Response Summary 3
BF=budesonide/formoterol; EMEA=European Medicines Agency; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with adverse event; N=number of patients in treatment group; PT=preferred term; SOC=system organ class
Note: Patients are counted only once in each preferred term category, and only once in each SOC category.

## *Serious adverse events*

Overall in the total study population, there were no deaths and a total of 4 (<1%) patients had serious adverse events during the treatment period; 3 (1%) patients receiving BF TURBOHALER 200/6 mcg and 1 (<1%) patient receiving BF SPIROMAX 160/4.5 mcg.

In the adolescent age subgroup, there were no serious adverse events reported in either the BF SPIROMAX or the BF TURBOHALER treatment group.

## *Discontinuation due to adverse events*

Overall in the total study population, there were a total of 4 (<1%) patients who discontinued from the study due to adverse events; 2 (<1%) patients in each treatment group.

In the adolescent age subgroup, there were no adverse events resulting in study discontinuation in either the BF SPIROMAX or the BF TURBOHALER treatment group.

### *Post marketing experience*

Post-marketing safety data for the adolescent age group has been collected since the original marketing authorization for DuoResp Spiromax as part of routine periodic safety update reports (PSURs). The available IQVIA MIDAS Health data from 2014 to the end of first half of 2019 for European Union 5 countries (France, Germany, Italy, Spain, and United Kingdom) show that there were over 34,000 off-label prescriptions to patients aged 12 through 17 years, accounting for the significant exposure in this population (0.43% to 1.59% of all yearly prescriptions). However, there were no safety signals or issues found in this population based on the post-marketing data.

## 2.5.1. Discussion on clinical safety

No new studies were submitted as a part of this variation, which is considered acceptable by CHMP.

The MAH provided 10 literature references to support this variation application.

*(4) Cates at al. Inhaled steroids with and without regular salmeterol for asthma: serious adverse events*

This review investigated the safety of salmeterol and therefore the relevance of this study in the context of this variation is low. In this review, there were no major safety concerns in children receiving ICS+LABA (salmeterol) combination as compared to adults.

*(7) Jorup et al. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma*

The incidence and type of AEs reported were similar for adolescents receiving BUD/FORM MART and those receiving comparator treatments. The proportion of adolescents experiencing a SEA or discontinuing due to an AE was very low and similar between treatment comparisons. All treatments were well tolerated and there were no adverse events with fatal outcomes reported among adolescents using BUD/FORM MART or comparators.

*(10) Ole D. Wolthers, Budesonide + formoterol fumarate dihydrate for the treatment of asthma*

Extensive evaluations have not indicated that inhaled budesonide in recommended doses in adults with asthma may cause clinically significant hypothalamic-pituitary-adrenal insufficiency and there are no data to suggest that this may be different with the FDC of budesonide-formoterol fumarate dihydrate.

Hypokalemia, hyperglycemia, and tachycardia are possible systemic effects of LABAs. Mortality and asthma-related SAEs, overall and cardiac SAEs, and discontinuations due to AEs were assessed in six double-blind, randomized clinical trials in 14,346 adolescents and adults with asthma during dry powder budesonide+formoterol fumarate dihydrate maintenance and reliever therapy for at least 6 months. The pooled data from the six trials showed that budesonide+formoterol fumarate dihydrate was well tolerated and was not found to be associated with an increased risk of death or cardiac-related SAEs or discontinuations due to AEs.

A recent analysis with additional data supported these observations. The tolerability profile of the FDC of budesonide+formoterol fumarate dihydrate appears to correspond with its individual components, the treatment being generally well tolerated with ≤10% of patients experiencing treatment-related AEs.

Oropharyngeal candidiasis, dysphonia, tremor, palpitations, and pneumonia were the most frequent complaints. Tolerability profiles would be expected not to differ between the commercially available dry powder combinations of budesonide+formoterol fumarate dihydrate. There were no tolerability profile head-to-head comparisons with other fixed combinations.

A randomized, double-blind, double-dummy, crossover, placebo- controlled study assessed the acute tolerability of budesonide+ formoterol fumarate dihydrate in 14 patients with asthma in whom two inhalations of 160/4.5 µg twice daily and 10 additional doses adding up to a total daily dose of 1920 + 54 µg; or formoterol fumarate dihydrate 54 µg/day; or placebo on three separate study days. Statistically significant changes in serum potassium, pulse rate, blood pressure, QT interval, blood glucose, and plasma lactate occurring with budesonide+formoterol fumarate dihydrate treatment were considered clinically unimportant. The authors concluded that the fixed combination of budesonide+formoterol fumarate dihydrate was well tolerated at high doses such as might be used by patients using the combination inhaler for relief of symptoms of asthma.

In addition, the MAH discussed the results of a Phase 3b study (Study BFS-AS-306) to which 48 adolescents were enrolled.This study was a 12-week, multicentre, double-blind, double-dummy, randomized, controlled trial and the primary endpoint was the change from baseline in weekly average morning peak expiratory flow (AM PEF). Safety was assessed by evaluation of adverse events.

In relation to safety, no major issues were identified in this study.

The proportion of patients reporting adverse events and treatment-related adverse events was similar or lower for adolescent patients in the BF SPIROMAX treatment group when compared either to adolescent patients who received BF TURBOHALER, or to the adult (18 through 64 years) and senior (≥65 years) age subgroups treated with BF SPIROMAX.

Additionally, the number (%) of frequently reported adverse events (≥2%) in adolescent patients treated with BF SPIROMAX was low (3 [17%]) when compared both to adolescent patients treated with BF TURBOHALER (11 [55%]), or to adults 18 through 64 years (96 [40%]) or seniors 65 or older (18 [42%]) treated with BF SPIROMAX.

In the adolescent age subgroup, there were no deaths, no serious adverse events or adverse events resulting in study discontinuation reported in either the BF SPIROMAX or the BF TURBOHALER treatment group.

Furthermore, the MAH clarified that, post-marketing safety data that covered the adolescent age group has been collected since the original MA for DuoResp Spiromax. The available IQVIA MIDAS Health data from 2014 to the end of first half of 2019 for EU 5 counties (France, Germany, Italy, Spain, and United Kingdom) show that there were over 34,000 off-label prescriptions of DuoResp Spiromax to patients aged 12 through 17 years, accounting for the significant exposure in this population (0.43% to 1.59% of all yearly prescriptions). However, there were no safety signals or issues found in this population based on the post-marketing data.

Lastly, CHMP also considered that extrapolation of clinical safety data from adults to adolescents in the asthma indication was acceptable and provided further support on the safety of DuoResp Spiromax for the treatment of adolescent patients with asthma.

## 2.5.2. Conclusions on clinical safety

The use of DuoResp Spiromax in Adolescents patients is agreed by CHMP from a safety perspective.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted/was requested to submit an updated RMP version with this application.

The PRAC considered that the risk management plan version 3.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

### *Safety concerns*

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | None |
| **Missing information** | None |

### *Pharmacovigilance plan*

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.
No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed.

### *Risk minimisation measures*

The safety information in the proposed product information is aligned to the reference medicinal product.

## *2.7. Update of the Product information*

As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were made to sections 4.4 and 4.8 of the SmPC to align information with the reference medicinal product, Symbicort Turbohaler.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Greece, Island, Ireland and Malta.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The extension of the asthma indication to include adolescents aged 12 years and over for both the DuoResp Spiromax and BiResp Spiromax licenses, does not alter the safety/efficacy profile of the product.

# 3. Benefit-Risk Balance

DuoResp Spiromax was approved in the EU on 28th April 2014 for the use in Asthma for adults only. With this application, the MAH proposed to extend the use in Asthma for the Adolescents patients.

Based on the efficacy and safety of the BF combination in adults with asthma, CHMP considered that it is acceptable to extrapolate available clinical efficacy and safety data from adults to adolescents.

Furthermore, in the supportive 12-week study (BFS-AS-306), efficacy and safety in adolescent patients treated with BF SPIROMAX (160/4.5 mcg) were similar to those in adolescent patients treated with BF TURBOHALER (200/6 mcg) and were similar or better when compared to adult (18 through 64 years) or senior (65 years and older) patients treated with BF SPIROMAX. In relation to safety, no major issues were identified in this study. In addition, there were no safety signals or issues found in this population based on the post-marketing data.

Thus, the orally inhaled combination can be used in adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists; or in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

## *3.1. Conclusions*

The overall B/R of DuoResp Spiromax is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II, IIIA and IIIB |

Extension of Indication to include adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists; or in patients already adequately controlled on both

inhaled corticosteroids and long-acting β2 adrenoceptor agonists. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC have been updated and the labelling and Package Leaflet have been updated accordingly. In addition, Changes were made to sections 4.4 and 4.8 of the SmPC to align information with the reference medicinal product, Symbicort Turbohaler. The MAH also took the opportunity to make administrative updates to the Greek, Islandic, Irish and Maltese local representatives phone numbers in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.2. RMP version 3.3 is considered acceptable.

### *Amendments to the marketing authorisation*

In view of the data submitted with the type II variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan (RMP) are recommended.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'DuoResp Spiromax EMEA/H/C/002348/II/0033'.