PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom
AUTHORS	Voorham, Jaco; Roche, Nicolas; Benhaddi, Hicham; van der Tol, Marianka; Carter, Victoria; Van Boven, Job; Bjermer, Leif; Miravitlles, Marc; Price, David

VERSION 1 – REVIEW

REVIEWER	Federico Lavorini Department of Experimental and Clinical Medicine, Careggi University Hospital Florence, Italy
REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	This retrospective study, based on validated databases, aimed at investigating non inferiority of ICS/LABA FDC deliverd by Spiromax after switching from the same ICS/LABA combination deliverd by the Turbuhaler DPI. The Auhtors found that, in both asthma and COPD patients, switching to Spiromax was non inferior to the same treatment delivered by the Turbuhaler in terms disease control. Of note in asthma, but not in COPD, patients switched to Spiromax reported fewer exacerbations and SABA use than those who were not switched. Generally I found this study adequate; however, I have some concerns that the Authors need to address. The lack of any differences in secondary endopoints in COPD patients is of interest and requires discussion. Due to the retrospective nature of the study, reason(s) of switching from inhaler devices other than Spiromax to Spiromax should be reported and discussed. Page 6, lines 7-13 the sentence is unclear. Please clarify Figure 1. The combination delivered by the diskus is SF abnd not BF

REVIEWER	Kenneth Chapman University of Toronto
REVIEW RETURNED	28-Apr-2018

GENERAL COMMENTS	The investigators have done a non-inferiority comparison of patients switching to a new budesonide/formoterol inhaler as compared to those continuing on a legacy budesonide/formterol inhaler. There are several limitations to the study they have not addressed. Major comments:

	1. In setting up a non-inferiority study, the authors have not set a high bar for the new inhaler. The primary endpoint was freedom from exacerbations but 80% of the asthma population had been free of exacerbations for the year before entry. With a low exacerbation rate in the study population, finding a measureable change with the new inhaler would have been difficult indeed. 2. The authors have not designed their analysis to address a major confounding factor. They've described their study as a comparison of BF Spiromax to BF Turbuhaler but they could just as easily have described it as a comparison between patients whose anti-asthma prescriptions had been repeated, perhaps with little attention and evaluation by the physician, and patients whose prescriptions had been changed implying extra evaluation, discussion and teaching by the practitioner and practice nurse. Would a switch between any other ICS/LABA inhalers have yielded the same or better results? The data was available for the authors to examine the non-inferiority of other ICS/LABA shifts by comparison. 3. Yet another potential confounder to explain the findings would be practice differences inherent in the study design. Isn't it probable that practices frequently prescribing a newer inhaler as compared repeating a prescription for a long-available inhaler, are more up-to-date and more asthma interested practices? In short, did the authors select Spiromax-treated patients from practices more expert in respiratory management? Were any differences or improvements a marker of practice differences rather than inhaler differences? 4. The number of ICS/LABA inhalers dispensed was higher in the Spiromax group than in the Turbuhaler group. Is this the consequence of better compliance with an newly prescribed medication (something that decays over time)? Do the authors have any insight into the dosing instructions for these two types of inhalers? An obvious oversight is sharing with the readers the number of doses per inhaler. See also the question reliever use in Minor Comments. Minor comments: 1. The Teva Spiromax is not available in all countries and many readers outside the UK will be unfamiliar with the device. I learned from the introduction to the manuscript that the device resembles an MDI but that the device is a DPI. I would welcome further information. 2. If the Spiromax resembles an MDI and delivers a fast-acting bronchodilator, formoterol, is it possible that the decreased use of SABA was the result of some patients using the Spiromax as a quick reliever.

VERSION 1 – AUTHOR RESPONSE

Voorham J, et al. bmjopen-2018-022051: Real-world effectiveness evaluation of budesonide/formoterol Spiromax® for the management of asthma and chronic obstructive pulmonary disease in the United Kingdom

	Reviewers	Reply to Comment
	EDITOR	
0.1	Please complete and include a STROBE check-list, ensuring that all points are included and state the page numbers where each item can be found: the check-list can be downloaded from here: http://www.strobe-statement.org/?id=available-checklists	The completed STROBE check is included in the resubmission package
	REVIEWER 1: FEDERICO LAVORINI	
1.1	This retrospective study, based on validated databases, aimed at investigating non inferiority of ICS/LABA FDC delivered by Spiromax after switching from the same ICS/LABA combination delivered by the Turbuhaler DPI. The Authors found that, in both asthma and COPD patients, switching to Spiromax was non inferior to the same treatment delivered by the Turbuhaler in terms of disease control. Of note in asthma, but not in COPD, patients switched to Spiromax reported fewer exacerbations and SABA use than those who were not switched. Generally I found this study adequate; however, I have some concerns that the Authors need to address	We thank the reviewer for their thorough understanding and summary of our study, and time spent reviewing the manuscript
1.2	The lack of any differences in secondary endpoints in COPD patients is of interest and requires discussion	A discussion of differences between treatments for the secondary endpoints in the asthma and COPD subgroups has been added in the Discussion section. Possible reasons for the lack of treatment differences seen in the COPD group have been described
1.3	Due to the retrospective nature of the study, reason(s) of switching from inhaler devices other than Spiromax to Spiromax should be reported and discussed	Due to the retrospective study design, reasons for switching inhaler were not captured. Patients were included from practices considered to have a policy of BF Spiromax adoption. While this makes it likely that patients were switched for economic reasons, it cannot be excluded that some inhaler switches were induced by poor disease control. This has been discussed in a new paragraph within the Discussion section

1.4	Page 6, lines 7-13 the sentence is unclear. Please clarify	We have amended these lines to clarify that included patients who switched to BF Spiromax were registered at practices considered to have a policy of BF Spiromax adoption or wholesale change (i.e., the decision to switch was based on cost savings instead of clinical reasons)
1.5	Figure 1. The combination delivered by the diskus is SF and not BF	Figure 1 has been corrected to FS Accuhaler/Diskus for consistency with the text
	REVIEWER 2: KENNETH CHAPMAN	
2.1	The investigators have done a non-inferiority comparison of patients switching to a new budesonide/formoterol inhaler as compared to those continuing on a legacy budesonide/formoterol inhaler. There are several limitations to the study they have not addressed	We thank the reviewer for carefully reviewing our manuscript
2.2	In setting up a non-inferiority study, the authors have not set a high bar for the new inhaler. The primary endpoint was freedom from exacerbations but 80% of the asthma population had been free of exacerbations for the year before entry. With a low exacerbation rate in the study population, finding a measurable change with the new inhaler would have been difficult indeed	We appreciate the reviewer's comment regarding the non-inferiority level. The *a priori* non-inferiority level of –10% used in our study was considered relevant by the scientific committee of the study. This level has been described as the minimal clinically important difference for COPD exacerbations (Chapman KR, et al. COPD 2013;10:243–9). It has also been used both to examine RDC, the primary endpoint in our study (Price D, et al. J Asthma Allergy. 2014;7:31–51), and number of exacerbations (Price D, et al. Prim Care Respir J. 2013;22:439–448) in similar studies of asthma patients switching inhalers from real-life, primary care settings. This has been clarified in the Methods section (pg9).
2.3	The authors have not designed their analysis to address a major confounding factor. They've described their study as a comparison of BF Spiromax to BF Turbuhaler but they could just as easily have described it as a comparison between patients whose anti-asthma prescriptions had been repeated, perhaps with little attention and evaluation by the physician, and patients whose prescriptions had been changed implying	A new paragraph regarding the selection of study centers, reasons for switching, and the impact of additional evaluation/teaching by practitioners has been added in the Discussion section to discuss these salient points. In a pilot study performed by the authors (Benhaddi H, et al. ERS 2016 [abstract]), 76% of 114 patients were switched to BF Spiromax without consultation, suggesting that any

	extra evaluation, discussion and teaching by the practitioner and practice nurse. Would a switch between any other ICS/LABA inhalers have yielded the same or better results? The data was available for the authors to examine the non-inferiority of other ICS/LABA shifts by comparison	confounding created by additional physician teaching for those who switched versus those remaining on original therapy was limited in the overall patient population. Comparison with other ICS/LABA FDCs would have been useful to determine any differences due to pharmacological effect; however, there were insufficient patient numbers for such comparisons. A note to this effect has been added in the limitations paragraph
2.4	Yet another potential confounder to explain the findings would be practice differences inherent in the study design. Isn't it probable that practices frequently prescribing a newer inhaler as compared repeating a prescription for a long-available inhaler, are more up-to-date and more asthma interested practices? In short, did the authors select Spiromax-treated patients from practices more expert in respiratory management? Were any differences or improvements a marker of practice differences rather than inhaler differences?	The BF Spiromax switchers came from practices considered to have a policy of BF Spiromax adoption or wholesale change (identified as practices at which ≥5 patients change to BF Spiromax within a 3-month period). We have added in the Discussion section a paragraph describing the economic motivation, rather than clinical motivation, for practices in our study to switch inhaler, and the impact on the results
2.5	The number of ICS/LABA inhalers dispensed was higher in the Spiromax group than in the Turbuhaler group. Is this the consequence of better compliance with an newly prescribed medication (something that decays over time)? Do the authors have any insight into the dosing instructions for these two types of inhalers? An obvious oversight is sharing with the readers the number of doses per inhaler. See also the question reliever use in Minor Comments	We thank the reviewer for this observation. Although the number of FDC inhalers was higher in BF Spiromax switchers, the average daily dose of ICS was lower – please see Table 2. The information regarding the dosing instructions is an important omission and has now been added to the Patients and Study Design section
2.6	Minor Comments: The Teva Spiromax is not available in all countries and many readers outside the UK will be unfamiliar with the device. I learned from the introduction to the manuscript that the device resembles an MDI but that the device is a DPI. I would welcome further information	Further information regarding the date of marketing authorisation and the system whereby the drug is delivered has been added in the Introduction

2.7	If the Spiromax resembles an MDI and delivers a fast-acting bronchodilator, formoterol, is it possible that the decreased use of SABA was the result of some patients using the Spiromax as a quick reliever	The use of BF as both single maintenance and quick relief therapy (SMART) has been recommended as an improved method of using ICS/LABA in asthma (Chapman KR, et al. Thorax 2010;65:747–52; Thomas M, et al. Prim Care Respir J 2012;21:8–10). This recommendation is not device-specific; as such, the use of such a combined regimen would be likely to affect both treatment groups. Therefore, differential SABA use between the two groups could be driven by differences in the design of the two inhalers – in particular, that the Spiromax more closely resembles an MDI such as is typically used to deliver reliever medications. We have expanded upon this point in the Discussion section.

VERSION 2 – REVIEW

REVIEWER	Federico Lavorini Careggi University Hospital, Florence Italy
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The Authors have replied fully to the concerns and the paper is well improved. I recommend to accept it as it is.

REVIEWER	Kenneth Chapman University of Toronto, Canada
REVIEW RETURNED	06-Aug-2018

GENERAL COMMENTS	Factors that might have been confounded the study findings have been discussed thoroughly by the authors.