Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva Respimat			
Name of active ingredient: Tiotropium bromide (ATC code R03B B04)			
Report date: October 12, 2020	**Study number:** 0205-0537	**Version/Revision:** 1.0	**Version/Revision date:** October 12, 2020
Title of study:	Characteristics of patients initiating Spiriva Respimat in Asthma in the UK: a cross-sectional, non-interventional study based on the Clinical Practice Research Datalink		
Keywords:	Spiriva Respimat, asthma, characteristics, Clinical Practice Research Datalink, United Kingdom		
Rationale and background:	Asthma is a respiratory condition that causes symptoms of wheezing, shortness of breath, chest tightness and cough. [P18-03927] According to treatment guidelines, asthma patients at treatment step 3 and above treated with inhaled corticosteroids, often in combination with long-acting beta agonists. However, many patients continue to have symptoms despite the use of these agents. [P10-08936] In late 2014, Spiriva Respimat (tiotropium bromide), a long acting anticholinergic, was approved for treatment of asthma in the UK. Since this time, it has been approved for use in asthma patients in other countries including Japan and the United States. The current BTS/SIGN Guideline for the management of asthma recommends tiotropium by soft-mist inhaler as an alternate controller therapy at steps three, four and five of the asthma treatment paradigm, on top of inhaled corticosteroid (ICS)/LABA. [P18-03927] As tiotropium is the first of its class approved for the use in the treatment of asthma, it is important to identify patient clinical and socio-demographic characteristics of those who initiate this treatment as opposed to other available treatments. This type of study will allow us to evaluate potential channeling of prescribing to different patient populations.		
Research question and objectives:	The main objective of the study is to describe the clinical and socio-demographic characteristics of asthma patients prior to the initiation of Spiriva Respimat for the treatment of Asthma within a general clinical population using the Clinical Practice Research Database (CPRD). A secondary objective is to describe and compare the characteristics of asthma patients who initiated Spiriva Respimat to asthma patients who initiated a higher dose of ICS/LABA FDC, or leukotriene receptor antagonist (LTRA), or alternatively those who switched from the previous ICS/LABA FDC to a new ICS/LABA FDC.		

Study design:

This study is a cross-sectional assessment of asthma patients who initiated Spiriva Respimat, who initiated leukotriene receptor antagonist (LTRA), who received a higher dose of ICS/LABA FDC, or who switched to a new ICS/LABA FDC in asthma in the UK during the study period (September, 2014-December 31, 2017). (Non-interventional study based on existing data, NISed)

Setting:

All adult patients who had a diagnosis of asthma before the index date, who received ICS/LABA FDC treatment and who were new initiators of Spiriva Respimat or those who initiated a higher dose of ICS/LABA FDC, a LTRA, or alternatively, those switched to a new ICS/LABA FDC.

The index date was defined as the date of new initiation of Spiriva Respimat or the date of initiation of, or switch to, the treatments specified above.

Patients with a diagnosis of COPD as well as patients on any LAMA prior to the index date was excluded from the main analysis. In a sensitivity analysis, patients who had both asthma and COPD diagnoses were included in the study.

A history in the database of at least 1 year of continuous up-to-standard (UTS) registration in the CPRD prior to index date was required to determine indications of use and previous treatments.

Subjects and study size, including dropouts:

Study size justification was conducted before the study initiation. The study size was dependent on the uptake of Spiriva Respimat for asthma in the CPRD. Table 1 provides a range of estimates for different prevalence estimates of disease (or characteristics). The numerator represents the number of patients with the comorbidity of interest and the denominator represents the number of new users in the population. With 500 patients we would have adequate confidence intervals around these estimates.

Table 1. Precision of estimates for proportion measures

Number of New Users	95% Confidence Intervals for Various Prevalences of Diseases (%)				
	1%	2%	5%	7%	10%
500	0.4-2.3	1.1-3.6	3.4-7.3	5.1-9.6	7.7-12.9
800	0.5-2.0	1.2-3.2	3.7-6.7	5.4-9.0	8.1-12.3
2,000	0.6-1.5	1.5-2.7	4.1-6.0	6.0-8.2	8.8-11.3
5,000	0.8-1.3	1.6-2.4	4.4-5.6	6.3-7.7	9.2-10.9

Before the study initiation, a feasibility check was conducted to assess the number of patients in the tiotropium group, after application of the study inclusion and exclusion criteria. The result indicated that between September 2014 and December 2017, the number of patients in the tiotropium group was around 935, which was sufficient for the study aims, as per the described precision estimates.

Variables and data sources:

Patients in this study were grouped by type of treatment initiated or switched to, including Spiriva Respimat, a higher dose of ICS/LABA FDC, a new ICS/LABA FDC or an LTRA. Patient characteristics were identified based on data recorded on the index date (date of dispensing/initiation of the exposure), or when a characteristic was not recorded on the index date, during the pre-index period (the one closest to the index date).

The primary outcome was whether a patient has a cardiac arrhythmias diagnosis on the index date or in the year prior to the index date. This was

	before patients initiated or switched to, including Spiriva Respimat, a higher dose of ICS/LABA FDC, a new ICS/LABA FDC or an LTRA. The secondary outcome was whether a patient had a cardiac failure diagnosis on the index date or in the year prior to the index date. In addition, the following covariates will be assessed in this study: • Demographic characteristics • Lifestyle factors • Asthma history and lab tests • Comorbidities • Concomitant prescriptions (both asthma related and non-asthma related prescriptions) This study was based on the United Kingdom's Clinical Practice Research Datalink (CPRD) GOLD database from September, 2014-December 31, 2017.
Results:	In total, the numbers of patients included in different groups in the main analysis are as follows: • The Spiriva Respimat group: 940 • The LTRA group: 4,509 • The ICS/LABA switcher group: 10,746 • The ICS dose increase group: 2,691 The average age of patients (in years, ±SD) on the index date was 54.22±15.74 in the Spiriva Respimat group, 49.12±16.30 in the LTRA group, 51.91±17.19 in the ICS dose increase group, and 53.31±16.96 in the ICS/LABA switcher group. The percentage of females was highest in the Spiriva Respimat group (69.47%), followed by the LTRA group (66.93%, ASD=0.054), the ICS/LABA switcher group (63.95%, ASD=0.117), and the ICS dose increase group (62.72%, ASD=0.142). Primary outcomes The primary outcome is whether patients had cardiac arrhythmias on or before the index date. Overall, 1.17% of the patients in the Spiriva Respimat group had cardiac arrhythmias on or before the index date, which was not different from that in the LTRA group (0.46%, ASD=0.079) and the ICS dose increase group (1.02%, ASD=0.013). The number of patient with cardiac arrhythmias on the index date or in the year prior to the index date in the ICS/LABA switcher group was less than 5 thus it was not reported and no ASD between the Spiriva Respimat group and the ICS/LABA switcher group was calculated.

	Secondary outcomes The secondary outcome is whether patients had Cardiac failure on the index date or in the year prior to the index date. The number of patients with cardiac failure in the Spiriva Respimat group was less than 5, thus this outcome was not reported and no ASD between the Spiriva Respimat group and the other groups was calculated.
Discussion:	This study showed that the percentage of UK asthma patients with cardiac arrhythmias was not different among those who initiated Spiriva Respimat, who initiated LTRA, and who increased the dose of ICS/LABA. No comparison was made for the secondary outcome (cardiac failure) among groups because the number of patients who initiated Spiriva Respimat was less than 5.
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH
Names and affiliations of principal investigators:	Dr. [redacted] [redacted]