1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto Respimat			
Name of active ingredient: Tiotropium+Olodaterol {R03AL06}			
Report date: 09 Jun 2023	**Study number:** 1237.0109	**Version/Revision:** 1.0	**Version/Revision date:** 09 Jun 2023
Title of study:	Safety profile of Tiotropium + Olodaterol used as maintenance treatment in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data		
Keywords:	Chronic Obstructive Pulmonary Disease (COPD), long-acting muscarinic antagonists (LAMA), long-acting beta 2-agonists (LABA), drug safety, secondary health data		
Rationale and background:	According to requirement by local regulatory authority, the safety information of newly approved drugs is to be collected to provide supplementary data to those identified in randomized clinical studies within 5 years after initial approval. This was a non-interventional study based on existing data and provided safety information of Spiolto (tiotropium+olodaterol) in ethnic Chinese patients with chronic obstructive pulmonary disease (COPD) in routine clinical practice in Taiwan. COPD is a leading cause of morbidity and mortality throughout the world and now is the third leading cause of mortality in China. The prevalence of COPD in China was 13.7% in population who were ≥40 years old. Spiriva Respimat® tiotropium 5µg once daily has been approved worldwide for over one decade and provides improvements on lung function and symptoms, and prevents exacerbations for patients with COPD. Olodaterol, a long acting β2–agonist (LABA), in the completed global clinical development for COPD, has shown a 24-hour duration of action profile, rapid onset of action, and an optimized inhaled LABA profile. Olodaterol at doses of 5µg once daily is safe and well tolerated. The combination of tiotropium and olodaterol in a single Respimat® Inhaler device provides a rational target for optimizing bronchodilator treatment of COPD, the safety and efficacy profile of which has been demonstrated in a large clinical development program with no concerns of any new safety issues comparing with placebo and its individual components. Chinese patients have participated in Tio+Olo Respimat® inhaler pivotal trials, and the safety findings are in line with those observed in the total trial population. Also, the efficacy is similar to that in the total trial population.		

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	In summary, the safety and efficacy profile of tiotropium + olodaterol (Tio+Olo) 5/5µg delivered via the RESPIMAT inhaler has been demonstrated in an entire completed global clinical program (Tio+Olo) with no concerns of any new safety issues for the compounds, their combination, and the indicated population.
Research question and objectives:	Primary objective: • To estimate the incidence rate of safety outcomes in Chinese patients with COPD who initiated Tio/Olo between 1st January 2014 and 31st December 2019; Secondary objective: • To compare the baseline characteristics of patients between those treated with Tio/Olo and those with other LAMA/LABAs Fixed Dose Combination (FDC) (Vilanterol/Umeclidinium; Indacaterol /Glycopyrronium) or (LABA: Salmeterol; Formoterol; Procaterol; Indacaterol; Olodaterol, LAMA: Tiotropium bromide; Glycopyrrolate; Umeclidinium) free combination;
Study design:	This study is a non-interventional cohort study based on existing data (NISed).
Setting:	Data used in this study came from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019. Inclusion criteria: 1. At least one prescription for Tio+Olo (FDC or free combination) as a new initiation between 1st January 2014 and 31st December 2019 (free combination defined as prescriptions of Tio and Olo on the same day); 2. Aged ≥ 40 years on the index date (date of first dispensing of Tio/Olo combined inhaler or free combination); 3. At least one diagnosis of COPD (ICD9: 491.x, 492.x, 496; ICD10: J41.x, J42, J43.x, J44.x) at any time prior to or on the index date; 4. At least one year of continuous health insurance coverage prior to

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the index date was required to allow for a look-back period to ascertain new use of the study drugs and to evaluate covariates of interest;

5. At least one health care encounter reimbursement in NHI.

Exclusion criteria:

1. Any use of Tio+Olo in free or fixed form within one year prior to the index date (free combination defined as prescriptions of Tio and Olo within 30 days of each other);
2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date.

Another cohort of patients using other LAMA/LABA (FDC or free combination) was identified to collect information of baseline characteristics, which was used to compare with that of patients treated with Tio+Olo. The Inclusion/Exclusion criteria of this cohort were similar to that for Tio+Olo cohort.

Inclusion criteria:

1. At least one prescription for LAMA+LABA FDC (Vilanterol/Umeclidinium; Indacaterol /Glycopyrronium) or free combination (LABA: Salmeterol, Formoterol, Procaterol, Indacaterol, or Olodaterol; LAMA: Tiotropium, Glycopyrrolate, or Umeclidinium) other than Tio/Olo as a new initiation between 1st January 2014 and 31st December 2019 (the free combination defined as prescriptions of the two individual compounds on the same day);
2. Aged ≥ 40 years on the index date (date of first dispensing of LAMA+LABA combined inhaler);
3. At least one diagnosis of COPD at any time prior to or on the index date;
4. At least one year of continuous health insurance coverage prior to the index date was required to allow for a look-back period to identify new use of study drugs and to evaluate covariates of interest;
5. At least one health care encounter reimbursement in NHI.

Exclusion criteria:

1. Any use of LAMA+LABA in FDC or free combination within

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	one year prior to the index date (free combination defined as prescriptions of two individual compounds within 30 days of each other); 2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date. A sensitivity analysis was performed for the Tio/Olo cohort, with the prior asthma exclusion criterion modified to exclude those with prior hospital diagnosis of asthma, while those with only non-hospital diagnosis of asthma were not excluded.
Subjects and study size, including dropouts:	As an observational study designed to describe incidence of selected adverse outcomes, there was no target study size and all eligible subjects who fulfilled the selection criteria were identified. From 2014 through 2019, 5,820 new users of Tio/Olo and 13,647 new users of LAMA/LABA were identified from Taiwan NHI.
Variables and data sources:	Exposures: Exposure of interest was new initiation of Tio/Olo or other LAMA/LABA inhaler (FDC or free combination) during the study period (between 1st January 2014 and 31st December 2019). Free form drug use was prescriptions of two individual compounds on the same day. Outcomes: Primary outcome: • Incidence rate of adverse events in patients with COPD treated with Tio+Olo (FDC or free combination on the same day) Secondary outcomes: • Secondary outcomes of interest were baseline characteristics of patients who initiated Tio+Olo or other LAMA/LABA from 2014 through 2019.

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Covariates:

Sex, age, calendar year of cohort entry, season of index date (December - February, March - May, June - August, September - November)

Additional characteristics were defined during the 1-year pre-index baseline period:

Prior COPD treatments, use of other respiratory drugs, previous acute COPD exacerbations, hospitalizations caused by COPD exacerbations, all-cause hospitalizations, comorbidities, Charlson Comorbidity Index (CCI), history of medications dispensed.

Data sources:

Data sources included Taiwan National Health Insurance (NHI), Taiwan Cancer Registry (TCR) and Taiwan Mortality Data.

Results:

Incidence rates of the adverse events of interest (Primary Outcome) are shown in the following table.

Adverse event	Incidence rate (per 100 person years)	95% Confidence interval
Potentially recurrent events		
Nasopharyngitis	10.63	(9.45-11.96)
Pneumonia[1]	0.55	(0.33-0.91)
Pneumonia[2]	0.84	(0.56-1.26)
Moderate COPD exacerbation	19.71	(18.05-21.52)
Severe COPD exacerbation	15.66	(14.21-17.26)
Constipation	17.06	(15.53-18.74)
Diarrhoea	1.58	(1.17-2.13)

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Urinary retention	6.17	(5.30-7.19)
Urinary tract infection[1]	2.53	(2.00-3.21)
Urinary tract infection[2]	9.44	(8.34-10.68)
Urinary tract infection[3]	13.54	(12.20-15.03)
Urticaria	6.96	(6.02-8.04)
Rash	0.69	(0.44-1.09)
Incident events (no occurrence of corresponding codes during the 1-year baseline period)		
Arrhythmia	6.80	(5.83-7.94)
Myocardial ischemia	4.02	(3.31-4.90)
Supraventricular tachycardia	0.33	(0.17-0.63)
Glaucoma	1.13	(0.79-1.62)
Nonfatal myocardial infarction[1]	0.59	(0.36-0.96)
Nonfatal myocardial infarction[2]	1.11	(0.78-1.59)
Nonfatal hemorrhagic stroke[1]	0.18	(0.08-0.44)
Nonfatal hemorrhagic stroke[2]	0.66	(0.42-1.05)
Nonfatal ischemic stroke[1]	1.03	(0.71-1.50)
Nonfatal ischemic stroke[2]	1.67	(1.25-2.24)
Nonfatal, Acute, but ill-defined, cerebrovascular disease[1]	0	
Nonfatal, Acute, but ill-defined, cerebrovascular disease[2]	0	
Death	19.15	(17.58-20.85)

[1] Diagnosis codes were primary inpatient diagnosis associated with a hospitalization

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[2] Diagnosis codes were primary or secondary diagnosis associated with a hospitalization

[3] Diagnosis codes were primary or secondary diagnosis associated with a hospitalization OR diagnoses codes associated with at least two outpatient/emergency visits within 30 days of each other

As for the overall summary on adverse events, among the 5,820 patients who received Tio/Olo, 498 were found to have moderate COPD exacerbation, 406 had severe COPD exacerbation, and 99 had myocardial ischemia. Different operational definitions were used for non-fatal myocardial infarction, non-fatal hemorrhagic stroke, and non-fatal ischemic stroke; using a more stringent criterion for each of these conditions, the number of patients who had these conditions were 16, 5, and 28, respectively. 526 patients were dead during the study period.

For secondary outcomes, various baseline demographic variables including sex, age, calendar year of cohort entry, seasons of index year and baseline clinical variables including previous COPD and other respiratory treatments, previous acute COPD exacerbation, hospitalizations, comorbidities and history of medications are shown separately in the main body, among which the secondary outcomes (events that occurred before index date) with significant difference between the two cohorts and may be related to the primary outcome are reported as follows: prior COPD treatment, prior use of respiratory drugs, prior COPD exacerbations, number of hospitalizations, history of cardiovascular disease, history of cerebrovascular disease, and history of use of cardiovascular medications. Due to the large of items evaluated in the secondary outcomes, not all of them are presented in the synopsis.

For the 5,820 new users of Tio/Olo, 5,210 received FDC and 610 received the free form combination on the same day, 89% of them were males and the median age was 72 (Interquartile range (IQR): 19 [63-82]). For the 13,647 new users of LAMA/LABA, 13,132

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	received FDC and 515 received the free form combination on the same day, 90% of the new users were males and the median age was 69 (IQR: 17 [61-78]). Comparing those who received Tio/Olo and those who received other LAMA/LABA, patients who initiated Tio/Olo had higher prevalence of two or more episodes of moderate or severe COPD exacerbations during the year before index date than patients who initiated other LAMA/LABA (4.8% vs. 2.3%). The Tio/Olo patients were more likely to be hospitalized because of COPD exacerbation during the year before index date than patients who initiated other LAMA/LABA (5.9% vs. 3.6%). Tio/Olo patients were more likely to be hospitalized two or more times for any reason during the year before index date than patients taking other LAMA/LABA (19.0% vs. 10.8%). Mean score of the Charlson Comorbidity Index was higher among the Tio/Olo patients than that among the patients on other LAMA/LABA (1.33 vs 0.97). With the modified selection criteria with regards to prior asthma diagnosis, 10,058 Tio/Olo new users were identified (patients with prior hospital diagnosis of asthma were excluded). The side effects profile among these patients was similar to that observed among the main analysis.
Discussion:	In this retrospective cohort study in Taiwan, safety profiles among more than five thousand COPD patients were evaluated. The findings from this study need to be interpreted cautiously along with safety data from clinical trials because of the difference of the baseline characteristics which means Tio/Olo users were slighter older, had more comorbidity and were less healthy in comparison with the other LAMA/LABA users as well as the those in clinical trials. It is not appropriate to directly compare the incidence of AEs, e.g., arrhythmia, myocardial ischemia and mortality in this study with those from other studies.
Conclusion:	The baseline characteristics of patients who initiated Tio/Olo in this study were different from patients who initiated other

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	LAMA/LABA as well as patients who initiated Spiolto in other studies. Generally, Tio/Olo users were older, had more comorbiditiesy and were less healthy. It is not appropriate to directly compare the incidence of AEs in this study with those from other studies. The general interpretation of this observational study is that the safety profiles observed in this study were in line with the established safety profile from the clinical trial program and the global safety experience for Tio/Olo.		
Marketing Authorisation Holder(s):	[redacted]		
Names and affiliations of [redacted] investigator:			