Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: *Spiolto® Respimat®* *2.5 microgram/2.5 microgram per puff inhalation solution*			
Name of active ingredient: *R03AL06 tiotropium bromide and olodaterol*			
Date of Synopsis: 19 Sep 2022	**Study number:** 1237-0087	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	*EVELUT®:* Assessment of dyspnea and other symptom burden as patient reported outcomes (PRO) in patients with chronic obstructive pulmonary disease (COPD), symptomatic on LABA/ICS maintenance therapy (now) treated with Spiolto® Respimat® (tiotropium/olodaterol) in comparison to open or fixed triple combination treatment (LAMA+LABA+ICS) in routine clinical practice.		
Keywords:	Chronic Obstructive Pulmonary Disease, symptom burden, dyspnea, LABA/ICS, Spiolto® Respimat®, triple therapy, patient reported outcome		
Rationale and background:	Dyspnea is the most relevant symptom burden leading to diagnosis, therapy initiation or change of maintenance COPD therapy. Clinical studies have demonstrated that the LAMA-LABA combination Spiolto® Respimat® significantly improves dyspnea in COPD patients. However, at the time of study planning no prospective clinical evidence was available supporting a direct switch from LABA/ICS to LAMA/LABA instead of moving to triple therapy if there is no indication for an ICS. Therefore, this non-interventional study (NIS) aimed to investigate if patients who were symptomatic (dyspneic) under LABA/ICS treatment could be switched to LAMA/LABA (Spiolto® Respimat®) at the discretion of their physician and do no worse as compared to triple therapy.		
Research question and objectives:	The primary objective of this NIS was to investigate the comparative effectiveness of Spiolto® Respimat® vs any free or fixed triple therapy in reducing dyspnea (as measured via mMRC (Modified Medical Research Council) questionnaire) and symptom burden (as measured via CAT™ (COPD Assessment Test)) in COPD patients who were dyspneic despite LABA/ICS maintenance treatment when switched to either Spiolto® Respimat® or to any triple therapy (free or fixed-dosed) by their attending physician in a real-world setting. Primary endpoints:		

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	• Difference in mMRC (modified Medical Research Council) score at baseline and after end of observation (approx. 12 weeks of treatment, Visit 2) • Difference in CAT™ (COPD assessment test) score at baseline and after end of observation (approx. 12 weeks of treatment, Visit 2) Secondary endpoints: • Patients' general condition according to the Physician's Global Evaluation (PGE) score at baseline and end of the observation period after of approximately 12 weeks, • Patient satisfaction with inhaler and therapy at end of observation period according to a seven-point ordinal scale • Proportion of mMRC responders with (ΔmMRC ≥1) and proportion of CAT responders with (ΔCAT ≥2)
Study design:	Open-label comparative multicentric cohort study according to §4, section 23 and §67, section 6 German Medicines Act, conducted in Germany (non-interventional study based on newly collected data). COPD patients being symptomatic despite LABA/ICS maintenance therapy were switched at visit 1 at the discretion of the attending physician to either Spiolto® Respimat® or any triple therapy (LABA+LAMA+ICS) according to clinical routine. Observational period was approximately 12 weeks after switch.
Setting:	This study was performed by Boehringer Ingelheim Pharma GmbH & Co. KG. The coordinating investigator was [redacted] Germany). The study was submitted to the Ethics committee of the State Medical Association of [redacted] on April 10, 2019 and was finally approved on May 29, 2019. It was planned to collect data of approximately 900 patients between Q2 2019 and Q2 2020 from approximately 150 sites in Germany. However, due to the Corona pandemic, site and patient recruitment was slower than

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	expected. After a one-year extension of the recruitment period, recruitment was stopped with 463 patients in 49 sites. All sites were medical practices (general practitioner, internal specialists and pulmonologists) with experience in treating COPD patients. Data collection started in July 2019 and was finished in September 2021.		
Subjects and study size, including dropouts:	Main inclusion criteria: • ≥40 years old COPD patients symptomatic regarding dyspnea (mMRC Dyspnea score ≥1) AND regarding symptoms (CAT™ Score ≥10) at the same time • Patients on LABA/ICS maintenance therapy switched to Spiolto® Respimat® or a free/fixed triple combination of LAMA + LABA + ICS at Visit 1 at the discretion of the treating physician. Main exclusion criteria: • Patients with contraindications acc. to SmPC • Acute exacerbation of COPD (within 4 weeks prior to Visit 1) • Frequently exacerbating patients, i. e. patients with ≥2 moderate exacerbations within the last 12 months or ≥1 exacerbation leading to hospitalization within the last 12 months • Acute respiratory failure (pH <7,35 and / or respiratory rate >30/min within 3 months prior to Visit 1) • History or current diagnosis of asthma and asthma-COPD overlap, history of allergic rhinitis within the last 5 years 469 patients were screened, 463 patients were recruited, completed visit 1 and received at least one dose of study medication (**Treated Set (TS)**, 329 in the Spiolto® Respimat® arm and 134 in the triple therapy arm). 46.4% women and 53.6% men were enrolled in the TS. Median age of TS patients was 66.0 years (range 39.0-90.0). 24 of 463 patients were excluded due to violations of at least one in- and/or exclusion criteria. One patient still had an open critical query at data base lock, possibly classifying as protocol violation, leading to 438 patients in the **Per Protocol Set** (309 in the Spiolto® Respimat® arm and 129 in the triple therapy arm).		

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	432 of 463 treated patients completed the study by performing visit 2 (303 of 329 in the Spiolto® Respimat® arm and 129 of 134 in the triple therapy arm). A total of 31 patients dropped out. Of the 432 patients within the Treated Set, 418 patients have filled in the mMRC and CAT™ questionnaires at visit 1 and visit 2. The 438 patients of the Per Protocol Set were used to match patients between the two treatment groups. For adjustment, the following covariates were used: patient demographics (age, sex), disease parameters (baseline CAT™ and mMRC), risk factors of COPD (pack-years of smoking) and physician specialization (GP / pulmonologist / Internal Specialist). It started with a 1:1 matching, but also a 1_{Triple}:$2_{Spiolto}$ and 1_{Triple}:$3_{Spiolto}$ matching was performed. 1:1 matching included 242 patients (121 each in the triple therapy and the Spiolto® Respimat® arm), 1:2 and 1:3 matching encompassed 320 patients (121 in the triple therapy arm, 199 in the Spiolto® Respimat® arm) and 347 patients (121 in the triple therapy arm, 226 in the Spiolto® Respimat® arm), respectively.		
Variables and data sources:	Data from medical records as well as patient's and physician's questionnaires were used as data sources. The following parameters were collected and assessed at visit 1 and/ or visit 2: - Specialization of attending physician (GP, pulmonologist, internal specialist), - Patient demographics (age, gender, height, weight), - History of COPD, - Rationale for changing COPD maintenance therapy, - Reported number and severity of exacerbations in the last 12 months - Number of exacerbations leading to hospitalization in the last 12 months - Device training (yes/no, reason for no training), - GOLD patient groups (A, B, C, D, calculated) based on GOLD guidelines 2019 - GOLD spirometric classification (1, 2, 3, 4) - Eosinophils in peripheral blood		

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	- Smoking history, current status (current smokers, former smokers, and never smokers) and pack-years - Concomitant diseases / comorbidities - Current (within the last 6 months) COPD related and other relevant concomitant medication at date of Visit 1 - Assessment of the severity of dyspnea based on the Modified Medical Research Council Questionnaire (mMRC), completed by the patient - Health and functional status by CAT™ questionnaire, completed by the patient - General condition of patient based on Physician's Global Evaluation (PGE) at the beginning and at the end of the study - Patient satisfaction with inhaler, inhalation, treatment and handling, according to a seven-point ordinal scale (ranging from very dissatisfied to very satisfied) - Safety: ADRs (serious and non-serious), fatal AEs, pregnancies during the study - Patient's willingness to continue or discontinue treatment with either triple therapy or Spiolto® Respimat® after the study (yes/no) - Rationale for treatment discontinuation (if applicable) All relevant data were documented in a pseudonymized manner in the electronic case report form (eCRF).
Results:	Results for all matched sets were generally similar, therefore results will mainly focus on the matched set 1:1 and the TS. <u>Primary endpoints:</u> At visit 1, TS patients in the Spiolto® Respimat® group and in triple therapy group had a mean mMRC score of 2.03 (SD 0.88) and 2.06 (SD 0.82), respectively. For patients of matched set 1:1, who were treated with Spiolto® Respimat® or triple therapy, a mean mMRC score of 2.07 (SD 0.80) and 2.07 (SD 0.81), respectively, was calculated. The mean improvement of mMRC score from Visit 1 to Visit 2 was higher in the Spiolto® Respimat® group of TS than in the triple therapy group,

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with a score reduction of 0.53 (CI 95%: 0.43-0.64) in Spiolto® Respimat® group, which is nearly twice the reduction in the triple therapy group (0.25 (CI 95%: 0.14-0.36)). Regarding matched set 1:1, mean reduction of mMRC score was comparable in both treatment groups (0.23 (CI 95%: 0.11-0.36) vs 0.25 (CI 95%: 0.13-0. 38)).

Mean difference between visit 1 and visit 2 between therapy groups yielded 0.28 (CI 95% 0.11-0.46) and -0.02 (CI 95% - 0.19-0.15) for TS and matched set 1:1, respectively.

Multivariable linear regression analysis with variable selection of TS for dependent variable 'change of mMRC score' showed that patients with worse baseline mMRC-score, higher age at registration and/or patients of general practitioners presented greater improvement in mMRC score. Baseline CAT™ score and pack-years of smoking only showed a weak influence on mMRC-score. 'Treatment' had no influence on change of mMRC score.

Regarding mean CAT™ score of TS patients at visit 1, patients in Spiolto® Respimat® and triple therapy group, respectively, had a mean score of 22.46 (SD 6.89) and 21.99 (SD 6.99). Mean CAT™ score of matched set 1:1 was 21.71 (SD 6.29) for patients in in Spiolto® Respimat® group and 21.79 (SD 6.72) for patients in triple therapy group.

Mean improvement of CAT™ score was greater in patients treated with Spiolto® Respimat® compared to patients in triple therapy group with the greatest difference between the treatment groups observed in the TS: 6.10 (CI 95%: 5.25-6.95) vs. 2.54 (CI 95%: 1.70-3.37) points for TS, and 3.45 (CI 95%: 2.45-4.45) vs. 2.51 (CI 95%: 1.62-3.40) for matched set 1:1. Multivariable linear regression analysis with variable selection for dependent variable 'change of CAT™ score' showed that patients of general practitioners had greater improvement of CAT™ score than patients of other specialists. Patients with worse CAT™ score at baseline and patients treated with Spiolto® Respimat® showed greater improvement in CAT™ score.

Secondary endpoints:

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PGE

At baseline TS patients of Spiolto® Respimat® group were in better condition than patients in triple therapy group: 49.5% of patients in Spiolto® Respimat® group had at least a good condition, whereas this was stated for 32.8% of patients in triple therapy group. At visit 2, percentage of patients with good or excellent condition has increased in both treatment groups. Increase was particularly great in Spiolto® Respimat® group for share of patients with excellent condition, from 5.8% at baseline to 25.4% at visit 2. Share of patients with good condition increased from 43.7% at baseline to 49.8% at visit 2. In the triple therapy group, increase from visit 1 to visit 2 in the percentage of patients with good and excellent condition was comparable (roughly 10 percentage points increase for each). Results for the matched set 1:1 were similar to those of TS.

Patient satisfaction with inhaler and therapy

Most of the patients in each group were overall 'very satisfied' and 'satisfied' with their treatment. Highest percentage of patients who were 'very satisfied' and 'satisfied' was observed in the triple therapy group using ≥2 products, followed by Spiolto® Respimat® group, followed by triple therapy group using 1 product (89.1% vs. 79.5% vs. 69.1%).

Regarding satisfaction with device in general, satisfaction with handling and satisfaction with inhaling >80% each in the Spiolto® Respimat® (82.8% - 85.1%) and the triple therapy group with at least 2 devices (88.2% -100.0%) and nearly 80% (77.0% - 78.6%) each in the fixed triple therapy group were very satisfied and satisfied in TS as well as in matched set 1:1.

Proportion of mMRC responders (ΔmMRC ≥1) and proportion of CAT responders (ΔCAT ≥2)

Percentage of TS patients who had a reduction of ≥1 in mMRC score was higher in the Spiolto® Respimat® group than in the triple therapy group (40.6% vs. 21.7%). In matched set 1:1, 25.0% and 21.8% of patients in in Spiolto® Respimat® and triple therapy group, respectively, had a reduction in mMRC score by at least 1 point.

Regarding CAT™ responders, 70.6% and 57.4% of TS patients in Spiolto® Respimat® and triple therapy group, respectively, had a decrease by ≥2 points in CAT score. In matched set 1:1, 67.9% of patients treated with

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	Spiolto® Respimat® and 56.3% of patients treated with triple therapy were CAT™ responders. Safety analysis: No ADRs or AEs with fatal outcome were reported by patients receiving triple therapy. No pregnancy occurred during the observational period in neither treatment group. No death was reported in neither treatment group. Seven patients in the Spiolto® Respimat® group (2.1%) reported one ADR each; 5 ADRs were of grade 1 (2 angina pectoris, 1 hypertension, 1 sinus tachycardia) and 2 ADRs of grade 3 (dyspnea). One of the 7 patients with an ADR (dyspnea of grade 3) reported overdosing of Spiolto® Respimat® treatment. One of the ADRs, hypertension of grade 1, was serious due to requirement or prolongation of the patient's hospitalization. No interim analysis was performed.
Discussion:	The study analysis is exploratory. Regarding the primary outcomes (mMRC and CAT score change), similar results were demonstrated for both treatment groups, meaning that symptomatic COPD patients not frequently exacerbating and having no history of severe exacerbations treated with LABA/ICS can be switched to LAMA/LABA without disadvantages compared to switching to triple therapy. For all analyzed patient groups, a reduction of mean mMRC scores and of CAT™ scores from visit 1 to visit 2 was observed which means improvement of dyspnea and symptoms. The results seem to show a trend for better outcomes with Spiolto® Respimat® regarding CAT™, which is a more sensitive measure than mMRC. Improvement of patient condition in both treatment groups was also shown by Physician's Global Evaluation (PGE) scores at visit 2. After approximately 12 weeks of treatment, the great majority of patients in both treatment groups were very satisfied or satisfied with treatment overall, handling of and inhaling from devices and the devices of the drugs in general, independent of used inhaler(s) and number of inhalers. Although it could be assumed that overall satisfaction with treatment would be higher with drugs in one single inhaler instead of multiple ones,

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EVELUT patients who used at least 2 products for triple therapy had a greater share of satisfied or very satisfied patients compared to those using a fixed triple therapy device. Perhaps patients felt to be better treated with several devices than only with one device. However, the triple therapy group of patients with three devices was small.

Regarding safety only few adverse drug reactions were reported. Seven patients in Spiolto® Respimat® treatment group (2.1%) and none of the patients in triple therapy group reported at least one ADR. Regarding this difference it has to be considered that the Spiolto® Respimat® group contained more patients than the triple therapy group (ratio about 2.5:1). 2.1% is less than observed in clinical trials, but in the same range as seen in non-interventional studies with Spiolto® Respimat®. In routine care investigators do not seem to enquire patients about AEs at visits and underreporting cannot be excluded. The seven ADRs reported in EVELUT were mainly cardiovascular events.

Conclusion

Triple therapy (LAMA/LABA/ICS) showed no additional benefit compared to Spiolto® Respimat® with regards to symptoms and health status as assessed by mMRC and CAT™ questionnaire.

This confirms the GOLD recommendation that dyspneic patients on LABA/ICS without an indication for ICS can be switched to a LAMA/LABA combination.

Improvement of patient condition in both treatment groups was also shown by Physician's Global Evaluation (PGE).

The great majority of patients treated with Spiolto® Respimat® or triple therapy was very satisfied or satisfied with treatments overall, inhaling and handling of the device(s) and the devices in general.

Regarding safety, there were only few drug-related AEs documented, most of them in line with the safety profile of Spiolto® Respimat®.

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Marketing Authorisation Holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Study Initiator: Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein		
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