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ORIGINAL RESEARCH

TRONARTO: A Randomized, Placebo-Controlled Study of Tiotropium/Olodaterol Delivered via Soft Mist Inhaler in COPD Patients Stratified by Peak Inspiratory Flow

Donald A Mahler[1,2]
Andrea Ludwig-Sengpiel[3]
Gary T Ferguson[4]
Alberto de la Hoz[5]
John Ritz[6]
Asif Shaikh[7]
Henrik Watz[8]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH, USA; [2]Section of Pulmonary Medicine, Valley Regional Hospital, Claremont, NH, USA; [3]KLB Gesundheitsforschung Lübeck GmbH, Lübeck, Germany; [4]Department of Medicine, Pulmonary Research Institute of Southeast Michigan, Farmington Hills, MI, USA; [5]Cardio-Metabolism and Respiratory, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [6]Biostatistics, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [7]Clinical Development & Medical Affairs, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; [8]Pulmonary Research Institute at LungenClinic Grosshansdorf, Airway Research Center North (ARCN), German Center for Lung Research (DZL), Grosshansdorf, Germany

Background: Inhaled bronchodilator therapy is currently the mainstay of treatment for patients with chronic obstructive pulmonary disease (COPD). Some inhalers require patients to achieve certain inhalation efforts either to activate the device or to deliver medication to the site of action. For dry powder inhalers, low peak inspiratory flow (PIF) can result in poor medication delivery but the clinical significance of this is not well understood.

Methods: TRONARTO was a 4-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group study which stratified patients with moderate-to-severe COPD according to their PIF against medium-low resistance at screening. Patients were randomized to receive tiotropium/olodaterol (5 µg/5 µg) or matched placebo delivered via the Respimat® Soft Mist™ inhaler (SMI). After 4 weeks of treatment, we assessed change from baseline in forced expiratory volume in 1 second (FEV_1) area under the curve 0–3 hours (FEV_1 $AUC_{0–3h}$) and trough FEV_1.

Results: Overall, 213 patients were randomized, of whom 106 received tiotropium/olodaterol (PIF <60 L/min, 55; PIF ≥60 L/min, 51) and 107 received placebo (PIF <60 L/min, 55; PIF ≥60 L/min, 52). For FEV_1 $AUC_{0–3h}$, the adjusted mean change from baseline versus placebo was 336 mL (95% confidence interval [CI] 246–425 mL; P<0.0001) in the PIF <60 L/min group and 321 mL (95% CI 233–409 mL; P<0.0001) in the PIF ≥60 L/min group. For trough FEV_1, the adjusted mean change from baseline versus placebo was 201 mL (95% CI 117–286 mL; P<0.0001) in the PIF <60 L/min group and 217 mL (95% CI 135–299 mL; P<0.0001) in the PIF ≥60 L/min group.

Conclusion: In the TRONARTO study, which included patients with moderate-to-severe COPD and varying inspiratory flow abilities, treatment with tiotropium/olodaterol resulted in significant lung function improvements versus placebo. This SMI can be used irrespective of the PIF that a patient can generate.

Keywords: inhaler, tiotropium/olodaterol, peak inspiratory flow, SMI, lung function

Plain Language Summary

People with chronic obstructive pulmonary disease (COPD) have difficulty breathing during activities of daily living. They sometimes experience worsening of their symptoms, known as a flare-up.

Inhalers are used to relieve symptoms and reduce the risk of a flare-up in people with COPD. To use a dry powder inhaler, you need to be able to breathe in "hard and fast" to break up the powder within the device. However, not all people with COPD can do this. With

Correspondence: Donald A Mahler
Medicine, Geisel School of Medicine at Dartmouth, Hanover, NH, USA
Tel +1 603 542-6777
Fax +1 603 543-5613
Email mahlerdonald@gmail.com

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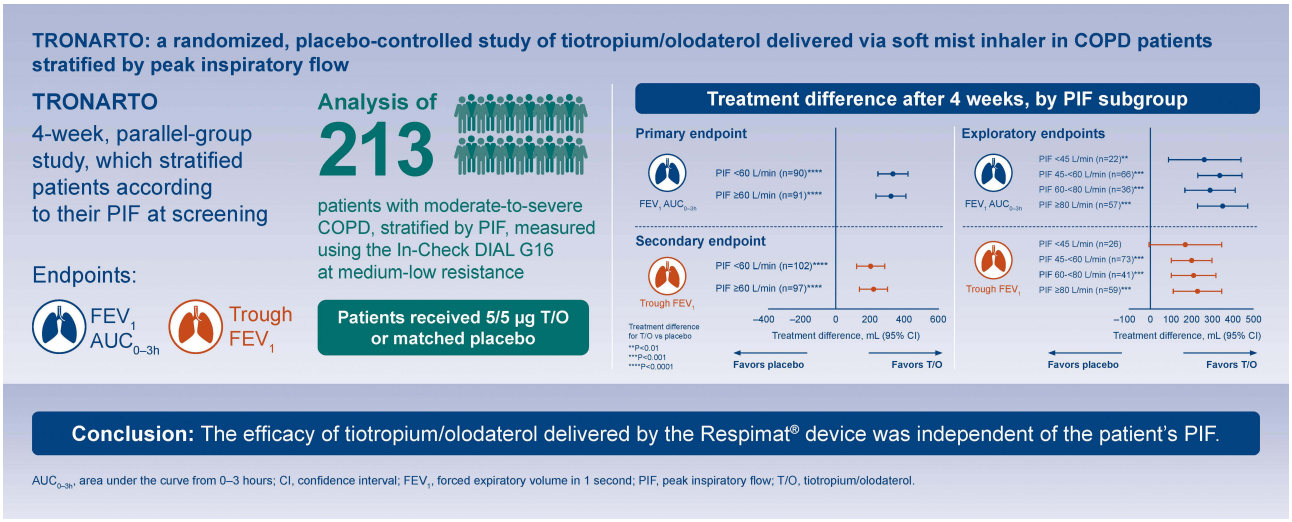
Graphical Abstract



the Respimat® Soft Mist™ inhaler (SMI), the person should take a slow, deep breath, and the mechanical energy released by pressing the dose-release button will help release the medication (called tiotropium/olodaterol) as a soft mist.

The TRONARTO study evaluated whether tiotropium/olodaterol SMI is suitable for all patients regardless of their ability to breathe in from an inhaler device. Subjects were given tiotropium/olodaterol or placebo using the SMI for 4 weeks. Changes in lung function were assessed after 4 weeks of treatment.

The results showed that regardless of people's ability to breathe in strongly, tiotropium/olodaterol treatment delivered using the SMI improved lung function compared with placebo.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease that requires maintenance treatment for symptom relief and exacerbation risk.[1,2] Inhaled bronchodilator therapy with long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), alone or in combination, is currently a mainstay of COPD treatment.[2–4] Correct use of inhalers and patient adherence to prescribed therapy are critical in order to achieve better clinical control and improved quality of life.[5]

There are many different inhalers available for the treatment of COPD, and delivery systems vary. The three handheld inhalation devices used in the treatment of COPD are dry powder inhalers (DPIs), pressurized metered-dose inhalers (pMDIs) and soft mist inhalers (SMIs).[5,6] The delivery and deposition of medication in the lungs by these devices is affected by both inhaler characteristics and patient-related factors, such as peak inspiratory flow (PIF).[6,7] DPIs, for example, require a PIF of >60 L/minute (low to medium-high resistance devices)[6,8–10] to overcome the inhaler's internal resistance and separate the medicine from its carrier particles.[11–14] Duarte et al reported that as many as one in five ambulatory patients with COPD have suboptimal PIF.[15] pMDIs operate independently of PIF but require the patient to coordinate inhaler activation with intake of breath.[5] Furthermore, they can be associated with high oropharyngeal deposition of larger particles.[5] SMIs use mechanical energy to generate a slow-moving mist of drug and require slow, coordinated inhalation.[5,16,17] Patient and modeled lung deposition profiles have shown that the SMI is associated with lower throat deposition and higher and more uniform deposition in the whole lung compared with DPIs and pMDIs.[18–20]

Tiotropium, a once-daily LAMA, and olodaterol, a once-daily LABA, are available as a fixed-dose combination delivered via the SMI.[21–24] This combination has been shown to reduce the risk of exacerbations and provide long-term improvements in lung function, dyspnea, exercise capacity and quality of life.[21,23] Tiotropium/olodaterol has been assessed in patients with different disease severities, demonstrating improvements in lung function, symptoms and quality of life across a broad population of patients with COPD.[21,25–27] In vitro/in silico data suggest that the SMI delivers high lung deposition even at low

modeled flow rates and across moderate-to-severe COPD inhalation profiles.[28] However, there are no data on the efficacy of tiotropium/olodaterol SMI in patients with COPD of different inhalation abilities. We anticipate no difference in outcomes according to PIF status.

The TRONARTO study stratified patients according to their PIF at screening. The aim of the TRONARTO study was to investigate the efficacy of inhaled tiotropium/olodaterol 5 µg/5 µg delivered via SMI on lung function in patients with moderate-to-severe COPD and different inhalation abilities (PIF ≥60 L/min or PIF <60 L/min against a medium-low resistance). Additional post hoc analyses were conducted on PIF subgroups.

Methods

Study Design

The TRONARTO study (NCT04223843) was a Phase IV, 4-week, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of patients receiving tiotropium/olodaterol (5 µg/5 µg) via the SMI.

At screening, patients were stratified by their PIF (PIF <60 L/min or PIF ≥60 L/min) using the In-Check DIAL G16 set at medium-low resistance. Following the screening visit, patients continued to receive their prescribed COPD medication; a 72-hour washout period (during which patients could use salbutamol rescue medication) was then implemented prior to randomization. Patients were randomized (1:1) to tiotropium/olodaterol 5 µg/5 µg or matching placebo using a validated system of pseudo-random number generation (approximately 50 patients per randomization block). Patients attended a clinic visit at Weeks 2 and 4, and a follow-up telephone call was conducted at Week 7.

The study protocol was reviewed and approved by the respective independent review boards and ethics committees of the participating sites: 26 in Germany and the United States of America beginning January 8, 2020 and ending September 29, 2020. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

Patients were included if they were aged 40 years or older with a diagnosis of moderate-to-severe COPD and were current or ex-smokers with a smoking history of >10 pack-years. Patients had a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity of <70% and a post-bronchodilator FEV_1 of ≥30–<80% of predicted normal at screening.

Patients were excluded if they had a significant disease other than COPD, defined by the investigator as any disease that could put the patient at risk, influence the results of the trial or raise concerns regarding the patient's ability to participate in the trial. Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids or hospitalization in the 6 weeks prior to Visit 1 or during the screening period were excluded, as were patients who experienced ≥2 moderate exacerbations that required treatment with antibiotics or systemic steroids or ≥1 exacerbation leading to hospitalization within the year prior to Visit 1. Those with a history of asthma or receiving inhaled corticosteroids in the 6 months prior to Visit 1 were also excluded.

Study Outcomes and Assessments

The primary endpoint was the change from baseline in FEV_1 area under the curve 0–3 hours (AUC_{0-3h}) at Week 4 for tiotropium/olodaterol vs placebo in each PIF stratum (PIF <60 L/min and PIF ≥60 L/min). The secondary endpoint was the change from baseline in trough FEV_1 at Week 4 for tiotropium/olodaterol vs placebo. PIF was measured three times at each clinic visit at both medium-low and high resistance and the highest PIF was used. In addition, patients also measured their PIF against medium-low resistance at home daily.

Post Hoc Analyses

Post hoc analyses were conducted to investigate which baseline patient characteristics showed an association with PIF when conducting a test for difference in patients with PIF <60 L/min and PIF ≥60 L/min.

In additional exploratory subgroup analyses, patients were sub-divided into PIF subgroups of PIF <45, PIF ≥45–<60, PIF ≥60–<80 and PIF ≥80 L/min. Analyses of percentage change from baseline for FEV_1 AUC_{0-3h} and trough FEV_1 were conducted in PIF subgroups PIF <60 L/min and PIF ≥60 L/min and in the PIF subgroups of PIF <45, PIF 45–<60, PIF 60–<80 and PIF ≥80 L/min.

Safety

For this analysis, safety and tolerability were assessed in a descriptive way based on adverse events (AEs), serious

AEs and physical examination. All AEs, whether serious or non-serious, that occurred during the course of the clinical trial were documented and reported by the investigators.

Randomization and Blinding

Patients, investigators, and everyone involved in trial conduct or analysis, or with any other interest in this study, were blinded regarding the randomized treatment assignments until after database lock.

Statistical Methods

For the primary endpoint, the adjusted means were calculated using an analysis of covariance model including the fixed categorical effects of treatment and the fixed continuous effect (FEV_1) of baseline.

The secondary endpoint was analyzed using the restricted maximum likelihood-based approach using a mixed model with repeated measures. The analysis of the secondary endpoint included the fixed, categorical effect of treatment at each visit and the fixed continuous effect (FEV_1) of baseline at each visit.

The study was designed to meet significance for primary and key secondary endpoints if significance was established for each stratum. A formal comparison on the magnitude of response between strata was planned.

The full analysis set (FAS) comprised patients who were randomized, received any dose of trial medication and who had both baseline and any evaluable post-baseline measurement for at least one of the efficacy endpoints, including FEV_1 $AUC_{0–3h}$ and trough FEV_1. The FAS was used for analysis of both the primary and secondary endpoints within the PIF <60 L/min and PIF ≥60 L/min groups. The TRONARTO study was not designed to detect differences in the primary or secondary endpoints between PIF subgroups. Because the primary endpoint only used baseline and Week 4 data, whereas secondary endpoints used baseline, Week 3 and Week 4, the number of patients in the FAS for the primary and secondary endpoints was different.

A sample size of 200 patients with a 1:1 randomization ratio was considered appropriate to provide adequate power to detect a treatment difference of 260 mL for FEV_1 $AUC_{0–3h}$ and to detect a treatment difference of 140 mL for trough FEV_1, with a standard deviation of 210 mL. Additional post hoc efficacy sensitivity analyses were conducted to adjust for age, gender and disease severity.

COVID

For patients who were unable to attend follow-up visits due to the COVID-19 pandemic and were thus not included in the efficacy analysis, missing data analysis using multiple imputation was conducted as an additional sensitivity analysis.

Results

Patient Disposition

In total, 213 patients were randomized (106 to tiotropium/olodaterol [PIF <60 L/min, 55; PIF ≥60 L/min, 51] and 107 to placebo [PIF <60 L/min, 55; PIF ≥60 L/min, 52]). At the end of the study period, 203 patients (95.3%) had received the full course of medication; 10 patients prematurely discontinued trial medication.

Of the 10 patients who did not receive the full course of trial medication, two patients withdrew due to an AE, two patients were lost to follow-up, two patients withdrew consent and four patients withdrew for "other" reasons (Figure 1).

Baseline Characteristics

Patient characteristics (by PIF stratum and by treatment) are shown in Table 1. In total, 110 patients were included in the PIF <60 L/min group (51.6% [tiotropium/olodaterol, 55; placebo, 55]) and 103 patients in the PIF ≥60 L/min group (48.4% [tiotropium/olodaterol, 51; placebo, 52]). Some differences in baseline characteristics were noted between PIF strata (Table 1).

Of the baseline characteristics shown in Table 1, there were differences in disease severity (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage), height, post-bronchodilator and percent predicted FEV_1 (all $P<0.05$) between the PIF <60 L/min and PIF ≥60 L/min groups. Some differences were also apparent for gender and age; we noted more females with PIF <60 L/min and the average age was higher in this group (both not significant).

Primary Endpoint: FEV_1 $AUC_{0–3h}$

For FEV_1 $AUC_{0–3h}$, 181 patients were included in the FAS. After 4 weeks of treatment with tiotropium/olodaterol, an improvement in adjusted mean FEV_1 $AUC_{0–3h}$ was observed in both the PIF <60 L/min (250 ± 33 mL, percentage improvement from baseline 20.3 ± 2.9) and PIF ≥60 L/min (333 ± 32 mL, percentage improvement from baseline 27.2 ± 2.4) PIF groups.

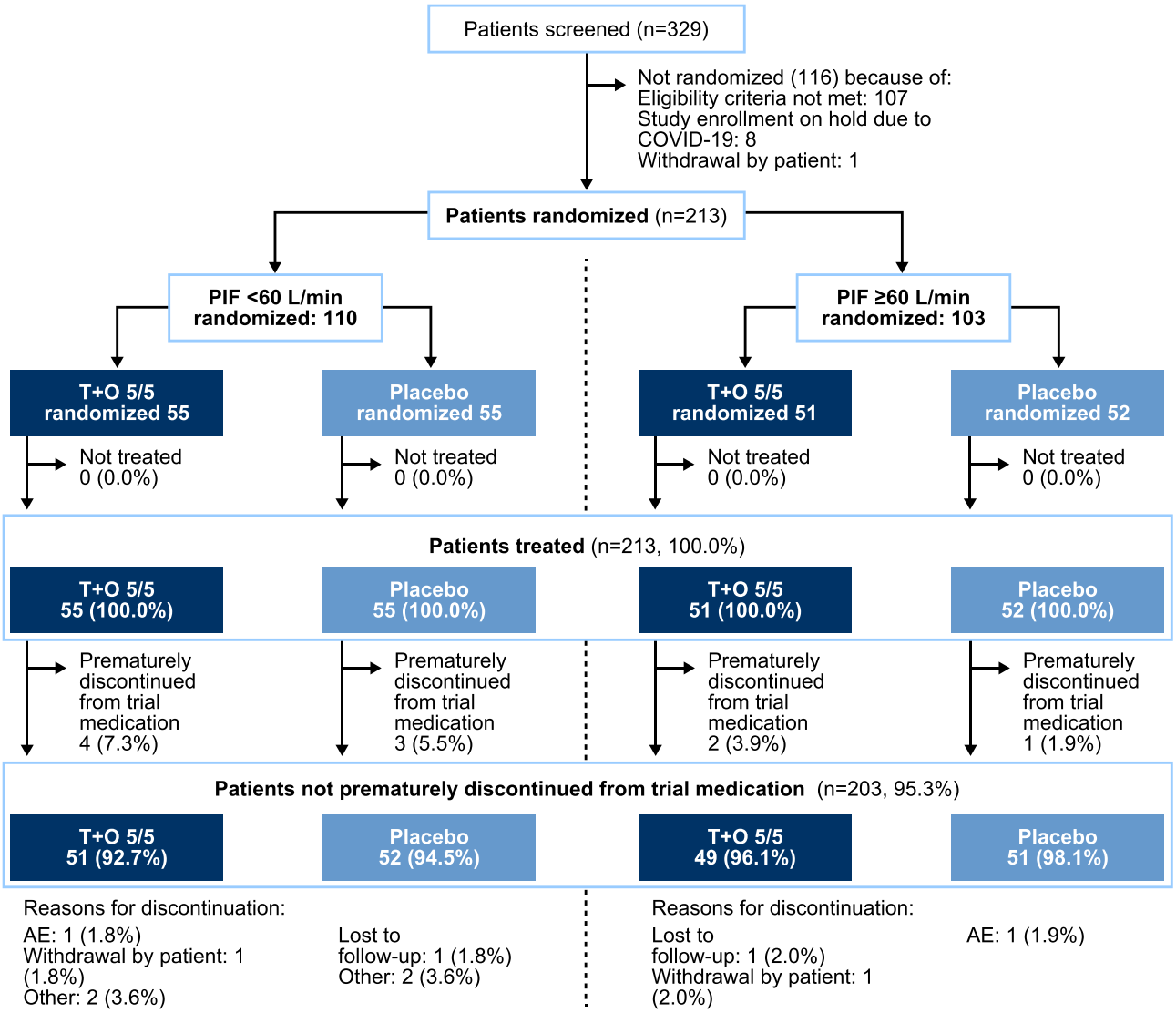


Figure 1 Patient disposition. Of the subjects in the treated set, 14 patients were excluded from the FAS (T+O, n=9; placebo, n=5) due to a lack of post-baseline efficacy measurements. The FAS (n=199) was used in the analysis of the secondary endpoint. For the primary endpoint, the FAS included n=87 patients treated with T+O and n=94 treated with placebo. Some patients excluded from the FAS also prematurely discontinued the study medication.
Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; FAS, full analysis set; PIF, peak inspiratory flow; T+O, tiotropium + olodaterol.

The treatment difference between tiotropium/olodaterol and matched placebo for FEV_1 $AUC_{0–3h}$ was 336 mL (95% confidence interval [CI] 246–425 mL; percentage improvement from baseline 24.1 ± 3.9) in the PIF <60 L/min group and 321 mL (95% CI 233–409 mL; percentage improvement from baseline 24.4 ± 3.4) in the PIF ≥60 L/min group (both analyses P<0.0001) (Figure 2A).

Secondary Endpoint: Trough FEV_1

For trough FEV_1, 199 patients were included in the FAS. After 4 weeks of treatment with tiotropium/olodaterol, an improvement in adjusted mean trough FEV_1 was observed in patients in both the PIF <60 L/min (95 ± 31 mL, percentage improvement from baseline 8.1 ± 2.7) and PIF ≥60 L/min (177 ± 30 mL, percentage improvement from baseline 15.2 ± 2.1) groups.

The treatment difference between tiotropium/olodaterol and matched placebo was 201 mL (95% CI 117–286 mL; percentage improvement from baseline 13.4 ± 3.8) for the PIF <60 L/min group and 217 mL (95% CI 135–299 mL; percentage improvement from baseline 16.0 ± 2.9) for the PIF ≥60 L/min group (both analyses P<0.0001) (Figure 2B).

Post Hoc Analyses

Baseline Characteristics

A post hoc sensitivity analysis was performed to adjust for age, gender and disease severity as some differences were seen within strata for these variables. The results for FEV_1

Table 1 Patient Characteristics by Treatment and by PIF

Characteristic	PIF <60 L/min n=110			PIF ≥60 L/min n=103		
	T/O (n=55)	Placebo (n=55)	Total (n=110)	T/O (n=51)	Placebo (n=52)	Total (n=103)
Sex, n (%)						
Male	27 (49.1)	18 (32.7)	45 (40.9)	27 (52.9)	32 (61.5)	59 (57.3)
Female	28 (50.9)	37 (67.3)	65 (59.1)	24 (47.1)	20 (38.5)	44 (42.7)
Age years, mean (SD)	64.00 (9.79)	67.05 (7.54)	65.53 (8.83)	62.80 (7.48)	65.88 (7.43)	64.36 (7.58)
BMI kg/m^2, mean (SD)	28.98 (5.77)	27.97 (5.14)	28.48 (5.47)	29.28 (6.25)	27.95 (6.59)	28.61 (6.43)
Height (cm), mean (SD)	169.25 (9.95)	165.79 (9.91)	167.52 (10.04)	171.54 (9.01)	173.19 (10.90)	172.37 (10.00)
Height categories (cm), n (%)*						
<160	9 (17.3)	18 (32.7)	27 (25.2)	5 (9.3)	7 (13.5)	12 (11.3)
160–<170	15 (28.9)	18 (32.7)	33 (30.8)	17 (31.5)	10 (19.2)	27 (25.5)
170–<180	19 (36.5)	11 (20.0)	30 (28.0)	21 (38.9)	19 (36.5)	40 (37.7)
≥180	9 (17.3)	8 (14.6)	17 (15.9)	11 (20.4)	16 (30.8)	27 (25.5)
Smoking history, n (%)						
Current	30 (54.5)	28 (50.9)	58 (52.7)	29 (56.9)	27 (51.9)	56 (54.4)
Former	25 (45.5)	27 (49.1)	52 (47.3)	22 (43.1)	25 (48.1)	47 (45.6)
Never	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline medication, n (%)						
≥1 pulmonary medication	47 (85.5)	46 (83.6)	93 (84.5)	40 (78.4)	38 (73.1)	78 (75.7)
LABA monotherapy	0 (0.0)	2 (3.6)	2 (1.8)	1 (2.0)	2 (3.8)	3 (2.9)
LAMA monotherapy	9 (16.4)	13 (23.6)	22 (20.0)	7 (13.7)	11 (21.2)	18 (17.5)
LAMA/LABA	26 (47.3)	20 (36.4)	46 (41.8)	14 (27.5)	12 (23.1)	26 (25.2)
SABA monotherapy	34 (61.8)	29 (52.7)	63 (57.3)	25 (49.0)	24 (46.2)	49 (47.6)
SAMA/SABA	1 (1.8)	2 (3.6)	3 (2.7)	4 (7.8)	5 (9.6)	9 (8.7)
Inhaler type used at study entry, n (%)						
DPI	26 (50.0)	25 (45.5)	51 (47.7)	20 (37.0)	23 (44.2)	43 (40.6)
pMDI	22 (42.3)	21 (38.2)	43 (40.2)	13 (24.1)	15 (28.8)	28 (26.4)
SMI	11 (21.2)	21 (38.2)	32 (29.9)	12 (22.2)	14 (26.9)	26 (24.5)
Lung function, mean (SD)						
Post-BD FEV_1, L	1.445 (0.430)	1.315 (0.462)	1.380 (0.449)	1.646 (0.462)	1.744 (0.513)	1.696 (0.488)
% predicted FEV_1	54.0 (12.3)	54.7 (13.9)	54.3 (13.1)	58.1 (11.2)	60.7 (12.1)	59.4 (11.7)
Mean PIF, L	49.9 (8.3)	47.8 (9.5)	48.8 (9.0)	80.6 (14.4)	85.3 (14.9)	82.9 (14.8)
Number of comorbidities, n (%)						
Cardiac disorders	19 (34.5)	23 (41.8)	42 (38.2)	9 (17.6)	19 (36.5)	28 (27.2)
Eye disorders	20 (36.4)	16 (29.1)	36 (32.7)	8 (15.7)	14 (26.9)	22 (21.4)
Gastrointestinal disorders	32 (58.2)	32 (58.2)	64 (58.2)	30 (58.8)	33 (63.5)	63 (61.2)
Immune system disorders	19 (34.5)	24 (43.6)	43 (39.1)	14 (27.5)	18 (34.6)	32 (31.1)
Infections and infestations	18 (32.7)	20 (36.4)	38 (34.5)	19 (37.3)	15 (28.8)	34 (33.0)
Metabolism and nutrition disorders	40 (72.7)	41 (74.5)	81 (73.6)	36 (70.6)	36 (69.2)	72 (69.9)
Musculoskeletal and connective tissue disorders	38 (69.1)	44 (80.0)	82 (74.5)	31 (60.8)	41 (78.8)	72 (69.9)
Nervous system disorders	30 (54.5)	23 (41.8)	53 (48.2)	25 (49.0)	29 (55.8)	54 (52.4)
Psychiatric disorders	28 (50.9)	27 (49.1)	55 (50.0)	27 (52.9)	28 (53.8)	55 (53.4)

(*Continued*)

Table 1 (Continued).

Characteristic	PIF <60 L/min n=110			PIF ≥60 L/min n=103		
	T/O (n=55)	Placebo (n=55)	Total (n=110)	T/O (n=51)	Placebo (n=52)	Total (n=103)
Reproductive disorders	20 (36.4)	13 (23.6)	33 (30.0)	14 (27.5)	12 (23.1)	26 (26.2)
Respiratory, thoracic and mediastinal disorders	55 (100.0)	55 (100.0)	110 (100.0)	51 (100.0)	52 (100.0)	103 (100.0)
Surgical and medical procedures	27 (49.1)	35 (63.6)	62 (56.4)	26 (51.0)	29 (55.8)	55 (53.4)
Vascular disorders	37 (67.3)	44 (80.0)	81 (73.6)	29 (56.9)	32 (61.5)	61 (59.2)
Other[†]	13 (23.6)	16 (29.1)	29 (26.4)	15 (29.4)	14 (26.9)	29 (28.2)
Regular home oxygen therapy, n (%)						
Y	4 (7.3)	1 (1.8)	5 (4.5)	1 (2.0)	1 (1.9)	2 (1.9)
N	51 (92.7)	54 (98.2)	105 (95.5)	50 (98.0)	51 (98.1)	101 (98.1)
GOLD stage, n (%)						
2 (moderate)	32 (58.2)	31 (56.4)	63 (57.3)	40 (78.4)	41 (78.8)	81 (78.6)
3 (severe)	23 (41.8)	24 (43.6)	47 (42.7)	11 (21.6)	11 (21.2)	22 (21.4)

Notes: A cut-off of 25% was used for the number of comorbidities. *Three patients in the T/O group were misclassified for height (PIF <60 L/min: n=52; PIF ≥60 L/min: n=54). [†]Other refers to patients who were denture wearers, edentulous, menopausal or postmenopausal.

Abbreviations: BD, bronchodilator; BMI, body mass index; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; PIF, peak inspiratory flow; pMDI, pressurized metered-dose inhaler; SABA, short-acting β_2-agonist; SAMA, short acting muscarinic antagonist; SD, standard deviation; SMI, soft mist inhaler; T/O, tiotropium/olodaterol.

AUC_{0-3h} and trough FEV_1 were consistent with the original efficacy results (Supplementary Table 1).

Exploratory Subgroup Analysis

Consistent with findings for PIF subgroups of PIF <60 and PIF ≥60 L/min, we noted an improvement in FEV_1 in patients receiving tiotropium/olodaterol compared with placebo when patients were stratified into PIF groups of <45, 45–<60, 60–<80 and ≥80 L/min. In these subgroup analyses for FEV_1 AUC_{0-3h}, all PIF subgroups reached P<0.01 (Figure 3A). For trough FEV_1, all PIF subgroups reached P<0.001 apart from PIF <45 L/min, which was the smallest subgroup in this analysis (Figure 3B). Further information on percentage change can be found in Supplementary Table 2.

Missing Post-Baseline Measurements

Of the patients who were excluded due to lack of post-baseline efficacy measurements, results from the missing data analysis showed that the results were similar when accounting for the missing data (Supplementary Table 3).

Safety

In total, 30 patients experienced an AE. Four patients experienced investigator-defined drug-related AEs, including dry mouth, dry tongue, cough, rhinitis and COPD, and two patients experienced AEs leading to discontinuation of the trial drug. The most common AEs were grouped under "respiratory, thoracic and mediastinal disorders" (tiotropium/olodaterol, n=5; placebo, n=7). These included COPD, allergic rhinitis, bronchiectasis, cough, dyspnea and epistaxis. AE profiles were similar between the treatment arms. Serious AEs resulting in hospitalization occurred in two patients treated with tiotropium/olodaterol (endometrial cancer and gastroenteritis [1.9%]) and in one patient receiving placebo (necrotizing fasciitis [0.9%]).

Discussion

The TRONARTO study, which included patients with moderate and severe COPD (GOLD 2 and 3), demonstrated that treatment with tiotropium/olodaterol for 4 weeks delivered via SMI resulted in a clinically significant improvement in lung function, irrespective of the PIF that the patient could generate.

In clinical practice, PIF is not routinely measured. The results from the TRONARTO study suggest that, when prescribing SMIs, measurement or consideration of PIF is not necessary. The SMI is an active device that does not rely on patient inhalation effort for activation or

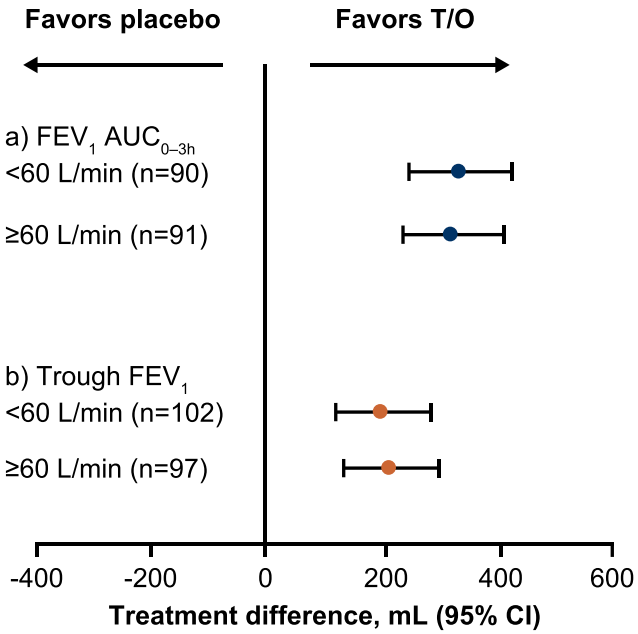


Figure 2 Treatment difference in (**A**) FEV_1 $AUC_{0–3h}$ and (**B**) trough FEV_1 after 4 weeks of treatment, by PIF subgroup (PIF ≥60 L/min vs PIF <60 L/min). FEV_1 $AUC_{0–3h}$ analyzed using an analysis of covariance model including the fixed categorical effects of treatment and the fixed continuous effect (FEV_1) of baseline. Trough FEV_1 was analyzed using the restricted maximum likelihood-based approach using a mixed model with repeated measures, including the fixed, categorical effect of treatment at each visit and the fixed continuous effect (FEV_1) of baseline at each visit.
Abbreviations: $AUC_{0–3h}$, area under the curve 0–3 hours; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; PIF, peak inspiratory flow; T/O, tiotropium/olodaterol.

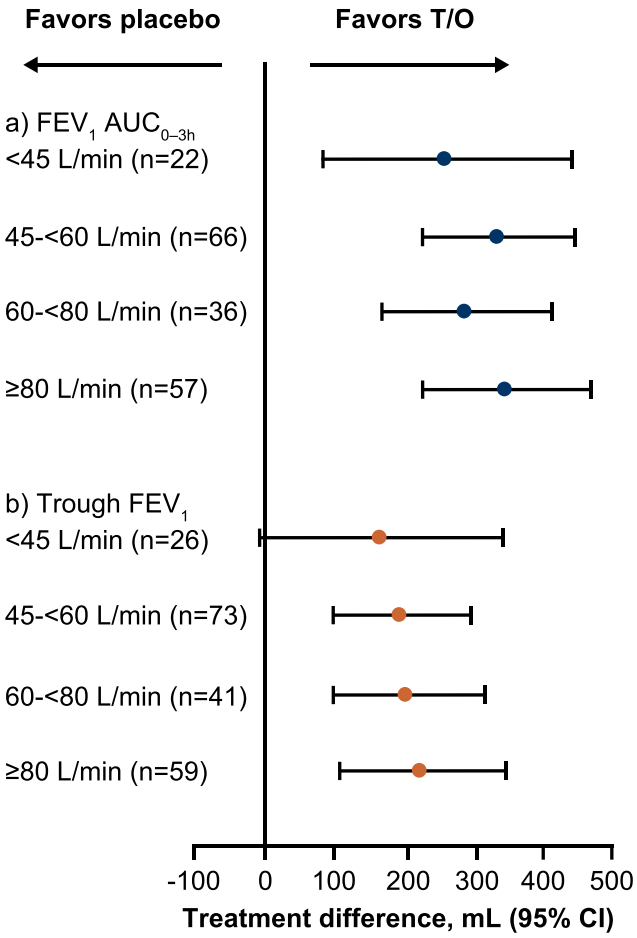


Figure 3 Treatment difference in (**A**) FEV_1 $AUC_{0–3h}$ and (**B**) trough FEV_1 after 4 weeks of treatment, by PIF subgroup (<45 L/min vs 45–<60 L/min vs 60–<80 L/min vs ≥80 L/min). FEV_1 $AUC_{0–3h}$ analyzed using an analysis of covariance model including the fixed categorical effects of treatment and the fixed continuous effect (FEV_1) of baseline. Trough FEV_1 was analyzed using the restricted maximum likelihood-based approach using a mixed model with repeated measures, including the fixed, categorical effect of treatment at each visit and the fixed continuous effect (FEV_1) of baseline at each visit.
Abbreviations: $AUC_{0–3h}$, area under the curve 0–3 hours; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; PIF, peak inspiratory flow; T/O, tiotropium/olodaterol.

release of the drug from the device;[29] it also has a very low internal resistance, and in vitro studies have demonstrated optimal lung deposition with the SMI at inspiratory flow rates of 15–30 L/min.[6] In this study, clinically significant lung function improvement was seen in all subgroups, from <45 L/min to ≥80 L/min.

Several studies of various inhaler types have extrapolated in vivo and in vitro modeling data to assume improvements in lung function at different inspiratory flow rates,[10,28,30,31] but clinical data to support these assumptions are limited. The efficacy of single bronchodilator therapy delivered via a handheld device in patients with different inhalation abilities has previously been reported,[32] but to our knowledge, this is the first study to investigate the relationship between PIF and efficacy in the context of dual bronchodilator therapy delivered via a handheld device.

In the current study, all patient subgroups showed clinically important improvements in lung function when treated with tiotropium/olodaterol delivered via Respimat SMI compared with those treated with placebo, which was also delivered via Respimat SMI. Patients with very low PIF may have benefitted from the SMI as this operates independently of PIF, delivering treatment over a longer time period. This supports in vitro data from Ciciliani et al, which found high lung deposition in patients using the Respimat SMI, regardless of PIF.[28]

Low PIF is a patient-related factor associated with suboptimal use of DPIs,[6,8,30,33] but there is limited evidence regarding its effect on lung function in patients with COPD. According to the GOLD 2021 strategy report, regular inhaler assessment is recommended and healthcare professionals should select the inhaler device that matches

the individual patient characteristics and ensure that patients continue to use their device correctly.[2]

In the TRONARTO study, there were numerically more female patients in the PIF <60 L/min cohort than in the PIF ≥60 L/min cohort, and the mean age was slightly higher in the PIF <60 L/min group (neither significant). This supports previous studies which have shown that female patients and older patients tend to have lower PIF.[7–9] Additionally, we noted a higher proportion of tall participants (>180 cm) in the PIF ≥60 L/min cohort than the PIF <60 L/min cohort, in line with previous studies that suggest an association between height and PIF.[8,34] Of note, there were more patients with severe COPD, according to GOLD classification, or a lower percent predicted FEV_1 in the PIF <60 L/min cohort.

The TRONARTO study has several strengths. This multicenter study included a large patient population, across a range of disease severities. The study was randomized, double-blind, placebo-controlled and included a parallel-group design. PIF was measured against a simulated resistance and not modeled or extrapolated from spirometry measurements. At the visits, patients were not informed of their PIF status, reducing potential performance bias. Furthermore, patients were trained in correct inhaler technique at two separate clinic visits, thereby reducing bias according to the patient's ability to use the SMI.

This study has some limitations. For example, symptom burden was not assessed, so it is unclear to what extent symptoms of COPD were associated with PIF status and the improvements in lung function. Placebo was used as the comparator for this study, which limited inclusion of very severe COPD patients (GOLD 4); additionally, patients with recent exacerbations and those taking inhaled corticosteroids were excluded.

Conclusion

In the TRONARTO study, treatment with tiotropium/olodaterol delivered via the SMI device resulted in significant lung function improvements versus placebo, irrespective of the PIF that a patient can generate. This indicates that PIF should not be a factor for healthcare professionals to consider when prescribing a soft mist inhaler.

Abbreviations

AE, adverse event; $AUC_{0–3h}$, area under the curve 0–3 hours; CI, confidence interval; COPD, chronic obstructive lung disease; DPI, dry powder inhaler; FAS, full analysis set; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-agonist; PIF, peak inspiratory flow; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler.

Data Sharing Statement

The data set used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the respective independent review boards and ethics committees of the participating sites: 26 in Germany and the United States of America beginning January 8, 2020 and ending September 29, 2020. A full list of participating sites in the study in this analysis is included in the supplementary file (Supplementary Table 4) and can be found at https://www.clinicaltrials.gov/ct2/show/NCT04223843. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Consent for Publication

All authors provide their consent for publication of this manuscript and all related contents. All patients provided their informed consent when entering the TRONARTO study.

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The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript, were involved at all stages of development and have approved the submitted manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agree to be

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