



Physical Functioning in Patients with Chronic Obstructive Pulmonary Disease Treated with Tiotropium/Olodaterol Respimat in Routine Clinical Practice in Italy

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ABSTRACT

Introduction: Clinical studies have shown significant improvements in exercise capacity in patients with chronic obstructive pulmonary disease (COPD) who are treated with a tiotropium/olodaterol fixed-dose combination (FDC). However, the effects of this treatment, which is administered in a single device, on physical functioning in a real-life setting of patients with COPD had not been fully determined.

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Methods: An open-label, observational study was conducted in 309 patients with COPD from 29 sites across Italy who received tiotropium/olodaterol FDC for 6 weeks. Physical functioning was evaluated using the Physical Functioning Questionnaire (PF-10). The primary endpoint was the proportion of patients with therapeutic success, defined as a ten-point increase in the PF-10 score from the baseline visit. Secondary endpoints were absolute changes in PF-10 score from baseline visit, the patient's general condition assessed by the Physician's Global Evaluation (PGE) score, and patient satisfaction with treatment, inhaling and handling of the device.

Results: According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) multimodality assessment, most patients were

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allocated to groups B (44.4%) and D (24.5%). Comorbidities were present in 73.9% of the patients. The primary endpoint was reached in more than half of the patients (52.5%), especially in groups B and D of GOLD. Patients' satisfaction with treatment, inhaling and handling of device was high, with a range of more than 86% to more than 89%, and very high in both groups B and D. The rates of drug-related adverse events were very low.

Conclusions: This real-life study showed that the tiotropium/olodaterol FDC treatment delivered via the Respimat device improves physical functioning and general patients' condition and is associated with a high degree of satisfaction and very low rates of drug-related adverse events, regardless of the group they belong to and their comorbidities.

Clinical Trial ID: NCT03003494.

Keywords: COPD; Exercise capacity; Fixed-dose combination; Health status; Inhaling device; Long-acting dual bronchodilation; Patient-reported outcomes; Olodaterol; Physical functioning; Tiotropium

Key Summary Points

Why carry out this study?

Tiotropium/olodaterol fixed-dose combination (FDC) improves exercise capacity in patients with chronic obstructive pulmonary disease (COPD).

The effects of FDC, administered in a single device, on physical functioning in a real-life setting had not been fully determined.

What was learned from the study?

Self-reported physical functioning and the general condition of COPD patients treated with tiotropium/olodaterol FDC via the Respimat device improved.

Both improvement and satisfaction were observed across all GOLD ABCD classification groups.

INTRODUCTION

Inactivity has a crucial role in the development of extra-pulmonary effects of chronic obstructive pulmonary disease (COPD), including skeletal muscle weakness, osteoporosis, and cardiovascular disease, and leads to an accelerated decline of lung function [1, 2] and an increased risk of hospitalization [3]. Moreover, a lower level of physical activity has the strongest predictive factor of death in patients with COPD [4] and are associated with poorer pulmonary outcomes and quality of life [5]. For this reason, the global initiative for chronic obstructive lung disease (GOLD) recommends that all patients with COPD participate in daily physical activity [6]. Despite this, the reduction of physical activity is very common in COPD, even starting from the GOLD stage I [7]. Several interventions can be established to increase physical activity and adequate bronchodilator inhalation therapy is one of the most important among them [8–10].

The GOLD document recommends administering a long-acting muscarinic antagonist (LAMA) with a long-acting beta-agonist (LABA) in patients not adequately controlled on a single long-acting bronchodilator treatment [6]. This has prompted the development of the LAMA + LABA fixed-dose combination (FDC) [11], which has been demonstrated to be safe and effective, and also fits the patients' needs.

Tiotropium/olodaterol is an inhaled FDC of the long-acting muscarinic antagonist tiotropium bromide and the long-acting β_2 -adrenergic agonist olodaterol, which was shown to improve pulmonary function, rate of exacerbation, patient-reported outcomes (such as dyspnea, use of rescue medication and health status), exercise capacity (e.g., endurance time) compared with placebo and its mono-components in several clinical trials and meta-analyses [12–24].

However, 'field-practice' studies have major importance for a comprehensive evaluation of treatments for COPD [25, 26]. The effectiveness of tiotropium/olodaterol in a field-practice scenario has been assessed in some observational studies, which have been conducted in Central

Europe and Japan [27–30]. However, further evidence from other countries is necessary, since treatment outcomes vary in different cultural and geographical areas [31]. Moreover, a detailed report of data on physical functioning and other relevant measures, such as health status and treatment satisfaction, may be relevant in the evaluation of any treatment for COPD [25].

We conducted an observational, prospective, multicenter study in Italy, which aimed to evaluate physical functioning, health status, and treatment satisfaction in patients with COPD who were treated with tiotropium/olodaterol FDC inhalation solution, during a 6-week routine clinical practice.

METHODS

Study Design

This open-label, prospective observational study was conducted in 29 pulmonary centers across Italy from July 2017 to May 2018. The study protocol was approved by the local institutional Ethics Committee (Comitato Etico Regione Calabria Sezione Area Centro) and written informed consent was obtained from each participant. This study is registered with ClinicalTrials.gov (NCT03003494) and was conducted in line with the Declaration of Helsinki.

Patients

Consecutive patients with COPD aged ≥ 40 years who required long-acting dual bronchodilation (LAMA + LABA) treatment with tiotropium/olodaterol were enrolled. Patients were excluded if they had known contraindications to tiotropium/olodaterol according to the Spiolto[®] Respimat[®] SmPC [32]. Patients who were in treatment with LABA plus inhaled corticosteroids were also excluded to avoid double LABA treatment. Patients who have been treated with a LABA/LAMA combination (free and fixed dose) in the previous 6 months were also excluded. Disease severity

according to GOLD multimodality assessment [6] was not considered as an eligibility criteria, but treatment was assigned according to clinical evaluation, as widely reported in the real-life setting, where patients follow a different therapy with respect to GOLD recommendations [33, 34].

Treatment

Patients were started on tiotropium/olodaterol FDC (5 μ g tiotropium + 5 μ g olodaterol) as an inhalation solution through the Respimat device for 6 weeks, which corresponded to the average time between two medical consultations. All patients were properly trained in using the Respimat device.

Variables

The following variables were collected and assessed at baseline (visit 1) and/or after the 6-week treatment (visit 2):

Visit 1:

- Demographic data
- Medical history on COPD (initial diagnosis), exacerbations in the last 12 months, as well as spirometry (performed either before or after initiation of treatment) and GOLD severity of obstruction at the time of visit [6]
- Smoking history and pack-years
- Concomitant diseases and medication
- Respiratory therapy: initiation of Spiolto[®] Respimat[®], treatment with other respiratory therapeutics (within 6 months prior to study treatment)
- Severity of dyspnea based on the modified Medical Research Council dyspnea scale [35]
- Physical Functioning Questionnaire (PF-10)
- General condition (assessed by Physician's Global Evaluation [PGE] score)

Visit 2:

- Changes in smoking history since visit 1
- Changes in concomitant diseases and medication since visit 1
- Respiratory therapy: regular use of Spiolto[®] Respimat[®] therapy (patient-reported)

adherence) and willingness to continue therapy, changes in other respiratory therapies since visit 1

- PF-10
- General condition (assessed by PGE score)
- Patient satisfaction survey
- Safety: adverse drug reactions associated with Spiolto[®] Respimat[®], as rated by the CTCAE, version 4.0.

The PF-10 questionnaire assesses ten subdomains about everyday physical activity and functioning of the validated 36-Item Short Form Health Survey (SF-36) [36]. PF-10 has previously been used in the COPD setting to measure physical functioning improvements in clinical practice [30]. Each PF-10 item may be answered with “yes, limited a lot”, “yes, limited a little”, or “no, not limited at all”, with a score of 1, 2 or 3, respectively. The scores for the 10 items were summed and transformed into a range of 0–100, with higher scores representing better physical functioning, according to Sauer et al. [30]. It can be easily completed within few minutes.

PGE is an eight-point scale in which the treating physician evaluated the patient’s general condition as poor (1–2), satisfactory (3–4), good (5–6) or excellent (7–8) [37].

Patients satisfaction was measured using a seven-point ordinal scale from very dissatisfied to very satisfied, referring to satisfaction with treatment, inhaling from the device and handling the device.

Endpoints

The primary endpoint of the study was the proportion of patients who achieve therapeutic success at visit 2, defined as a ten-point increase in the PF-10 score between visit 1 and visit 2. The threshold of ten-point change was based on the distribution-based method by Cohen [38]. Based on two 1-year studies conducted in patients with COPD, the baseline standard deviation for physical functioning scores was 22. The minimal important difference ranged between 4 and 11 [30]. Secondary endpoints were: (1) the evaluation of the absolute changes in PF-10 score from visit 1 to visit 2; (2) patient’s

general condition assessed by the PGE score at visit 1 and at visit 2; and (3) patient satisfaction with tiotropium/olodaterol at visit 2.

Data Analysis

Data were analyzed by descriptive statistics. Due to the intents of the study, no formal sample size calculation was performed. Data were analyzed in the overall population and according to the GOLD severity assessment [6].

Any patient who received at least one dose of tiotropium/olodaterol was included in the safety population. Demographic/baseline data were analyzed in the safety population. Patients in the safety population who had a PF-10 score at visit 1 and visit 2 comprised the full analysis set (FAS). All analyses were performed using the SAS 9.4 software.

RESULTS

Patients Characteristics

In total, 309 patients were screened, and 306 received tiotropium/olodaterol (safety population); the FAS population consisted of 278 patients (Fig. 1).

Table 1 depicts the baseline characteristics of the TS population. Mean age was 71 ± 9 years; 21.6% of the patients were younger than 65 years. Most patients ($n = 216$; 70.6%) were male. Most of them had a degree of severity of obstruction of grade II ($n = 137$; 44.8%) or III ($n = 84$; 27.5%) and modified Medical Research Council scores of 2 ($n = 93$; 30.4%) or 3 ($n = 80$; 26.1%). According to the ABCD multimodality assessment of the GOLD 2017 update, 44.4% of the patients were allocated to group B and 24.5% to group D. One exacerbation was reported in 40.5% of the patients of the TS, and two or three exacerbations occurred in 17.7% and 6.9% of the patients, respectively.

Mean PF-10 score was of 48.3 ± 26.0 (95% CI 45.2–51.4), and a PGE score was 3 ($n = 69$; 24.8%) or 4 ($n = 72$; 25.9%) in most patients, corresponding to a satisfactory general

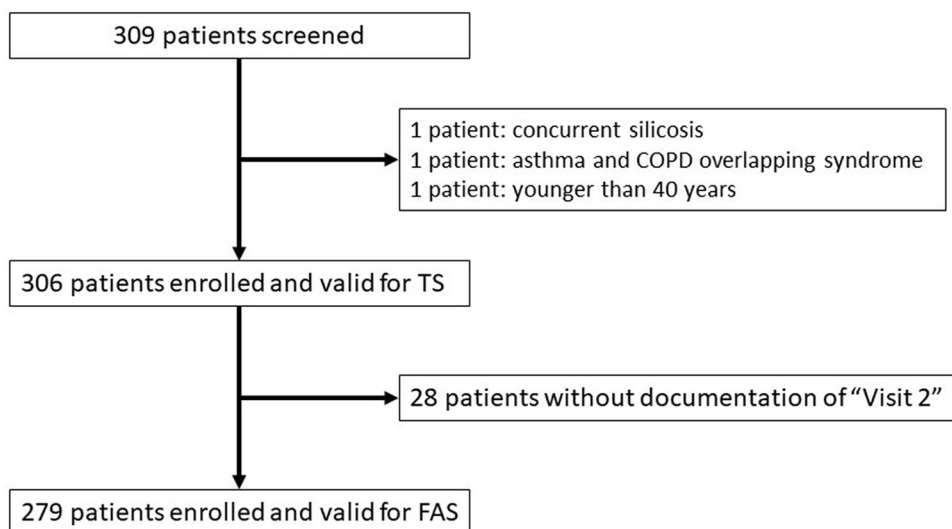


Fig. 1 Patient flow chart

condition (Table 1). A total of 190 patients (62.1%) were already taking therapy for COPD (Table 2).

Concomitant diseases were present in 73.9% of the patients who were included in the safety population, and 64.4% of subjects were treated with concomitant medications (Table S1). In the majority of cases (195 patients, 63.7%), the concomitant medications were continued during the study and in only four patients (1.3%) new prescriptions were issued at enrollment.

Therapeutic Success

Achievement of therapeutic success was reported in more than half of the patients in the FAS (52.5%; 95% CI 46.5–58.5%) (Table 3). When stratifying patients according to ABCD grouping, therapeutic success was achieved in 23.4% of patients in group A (95% CI 12.3–38.0), 60.0% (51.0–68.5) of those in group B, 40.0% (23.9–57.9) of subjects in group C, and 65.1% (52.4–76.5) of patients in group D (Table 3).

Change in PF-10 Score

The absolute median change of PF-10 score between visit 1 and visit 2 was of ten points (range, 60 to 80) with a mean change of 11.2 ± 21.2 points (95% CI 8.8–13.8) (Table S2).

Median changes from baseline were 5 (range, 60 to 60), 10 (range, 50 to 80), 0 (range, 45 to 45) and 10 (range, 25 to 75), in patients assigned to GOLD groups A, B, C, and D, respectively.

PGE Scores

Overall, PGE scores improved over the study period: at visit 2, PGE score was 6 in 40.7% of patients (Fig. 2). In a post hoc unplanned analysis, a positive relationship between PF-10 and PGE scores was found by Spearman's correlation analysis (Table S3).

Patients' Satisfaction

Most patients in the FAS ($n = 240$; 86.3%) were satisfied or rather satisfied with the tiotropium/olodaterol FDC treatment, as well as with the Respimat device (Table 4). Similar results were shown when stratifying patients according to disease severity (Table S4). In a post hoc unplanned analysis, a χ^2 test analysis indicated no significant correlation between age and patient satisfaction (treatment: $p = 0.230$; inhaling from device: $p = 0.500$; handling of device: $p = 0.075$) and among the four GOLD severity groups (treatment: $p = 0.212$; inhaling from device: $p = 0.170$; handling of device: $p = 0.505$).

Table 1 Demographics and clinical characteristics of the safety population at baseline (visit 1)

Data	Patients, <i>n</i> (%)^a
Number of patients	306
Age at enrollment (years)	
Mean \pm SD	71 \pm 9
Min–max	40–91
Median	72
< 65 years, <i>n</i> (%)	66 (21.6)
\geq 65 years, <i>n</i> (%)	240 (78.4)
Gender, <i>n</i> (%)	
Male	216 (70.6)
Interval between initial diagnosis of COPD and enrolment (years)	
Mean \pm SD	7.5 \pm 7.8
Min–max	0.0–48.0
Median	5.0
Severity of obstruction by spirometry	
1	41 (13.4)
2	137 (44.8)
3	84 (27.5)
4	42 (13.7)
Not available	2 (0.7)
mMRC Questionnaire	
Grade 0	24 (7.8)
Grade 1	71 (23.2)
Grade 2	93 (30.4)
Grade 3	80 (26.1)
Grade 4	38 (12.4)
COPD degree of severity according to the GOLD 2017 ABCD classification	
A	55 (18.0)
B	136 (44.4)
C	40 (13.1)
D	75 (24.5)
A/B pooled	191 (62.4)
C/D pooled	115 (37.6)
Number of exacerbations in the last 12 months	

Table 1 continued

Data	Patients, <i>n</i> (%) ^a
0	94 (30.7)
1	124 (40.5)
2	54 (17.7)
3	21 (6.9)
> 3	13 (4.2)
Physical Functioning Questionnaire (PF-10)	
Mean ± SD	48.3 ± 26.0
95% CI	45.23–51.36
Median (min–max)	50 (0–95)
Physician's Global Evaluation (PGE)	
1	2 (0.7)
2	5 (1.8)
3	69 (24.8)
4	72 (25.9)
5	65 (23.4)
6	46 (16.6)
7	19 (6.8)
8	0 (0)

^a Unless otherwise stated

Safety

In total, three investigator-defined drug-related AEs (grade 1 tremor, grade 1 urticaria and grade 3 hypertension) occurred in three patients (1%). All of these events have recovered and two of the events required treatment. One patient had a fatal AE (death) without a suspected causal relationship to the study treatment (Table S5).

DISCUSSION

Physical activity is recognized as a relevant measure of outcome in clinical studies of COPD, during programs of rehabilitation, and as patients' self-management [39]. Indeed, regular physical activity is also strongly recommended

by several guidelines of scientific societies for the maintenance of pharmacotherapy, in addition to other physical and social aspects of a healthier lifestyle for patients with this disease [6, 27].

In this prospective study, we described physical functioning as a surrogate, but easy to assess, proxy for physical activity and exercise capacity in patients with COPD who were treated with tiotropium/olodaterol FDC inhalation solution, during a 6-week routine clinical practice in Italy. Moreover, we evaluated the patient's general condition during therapy course; satisfaction with different aspects of the treatment were also determined. Remarkably, this observation period, albeit short, corresponds to the usual treatment time before assessing the efficacy of a new COPD treatment

Table 2 Previous respiratory treatments for COPD in the safety population 6 months prior initiation of the tiotropium/olodaterol Respimat

Previous respiratory treatments	<i>n</i>	%
Number of patients	306	100
Previous treatment with COPD therapy		
No	116	37.9
Yes	190	62.1
Respiratory therapeutics		
Short-acting beta-2 agonist	13	4.2
Long-acting beta-2 agonist	14	4.6
Short-acting anticholinergic	3	1.0
Long-acting anticholinergic	128	41.8
Short-acting anticholinergic/short-acting β -2 agonist in fixed combination	1	0.3
Long-acting beta-2 agonist + inhaled corticosteroid	63	20.6
Inhaled corticosteroid	11	3.6
Systemic corticosteroid	2	0.6
Theophylline	2	0.6
Prescription of previous respiratory COPD treatment		
Continuation of an existing regimen	3	1.0
New prescription at enrollment	1	0.3
Discontinued at enrollment	188	61.4

and this choice also limits the patients' dropout from the study. The number of exacerbators was unexpectedly high: however, the aim of our study was not to investigate the factors associated with exacerbations, which should be addressed in dedicated analyses.

Although with all the limitations of any observational, uncontrolled study, data showed improvements of the level of physical activity, with GOLD group D patients, presenting the more severe disease, showing the highest success rate, followed by patients assigned to group B and C. Intriguingly, the distribution of the therapeutic success of patients does not mirror the distribution of patients among COPD severity groups, according to the GOLD multimodality assessment. As a matter of fact, the best successful therapeutic outcome was observed in more symptomatic patients, who

were assigned to groups B and D. Patients assigned to groups A and C show less symptoms and more exacerbation, and are therefore less likely to benefit from tiotropium/olodaterol FDC inhalation solution.

These findings, collected in a population of patients enrolled in clinical practice, support previous evidence, which was collected in Central and Eastern Europe [27, 30, 37]. It may have major importance for clinical practice since therapeutic success is strongly associated with compliance and adherence of the patients [27, 40, 41]. Remarkably, these results were reported in patients showing multiple concomitant diseases, mainly affecting the cardiac, metabolic/endocrine, and/or vascular systems.

Our data also showed an improvement in the general state of the patient, as assessed by the PGE and the presence of a direct correlation

Table 3 Therapeutic success (ten-point increase in the PF-10 score between visit 1 and visit 2) stratified by GOLD multimodality assessment

GOLD groups	Therapeutic success	n (%)	95% CI
A	Therapy successful	11 (23.4)	12.3–38.0
	Therapy not successful	36 (76.6)	
B	Therapy successful	78 (60.0)	51.0–68.5
	Therapy not successful	52 (40.0)	
C	Therapy successful	14 (40.0)	23.9–57.9
	Therapy not successful	21 (60.0)	
D	Therapy successful	43 (65.1)	52.4–76.5
	Therapy not successful	23 (34.8)	
Total	Therapy successful	146 (52.5)	46.5–58.5
	Therapy not successful	132 (47.5)	

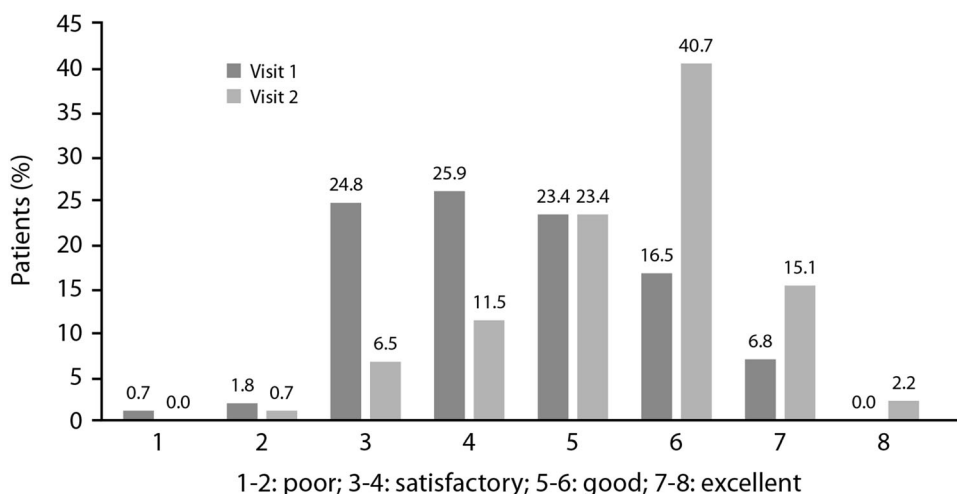


Fig. 2 Physician’s global evaluation (PGE) at visit 1 and visit 2. *FAS* full analysis set, *TS* treated set

between physical functioning and general conditions. Therefore, inhaled therapy with tiotropium/olodaterol FDC with the Respimat device also seems to be associated with improvements in the well-being of the subject.

Moreover, patients reported a high satisfaction with the treatment with tiotropium/olodaterol FDC inhalation solution, inhaling from the Respimat device, and handling of the device as well, which further supports other studies in different countries and, in some cases, those

that did not analyze patients with COPD exclusively [42, 43].

The overall satisfaction, combined with an improved physical functioning and general condition, may contribute to increase adherence to the prescribed medications [44], thus optimizing clinical outcomes. The once-daily dosing of the tiotropium/olodaterol FDC may also have contributed to the higher adherence compared with multiple daily doses [12].

Table 4 Patient satisfaction with Spiolto[®] Respimat[®]

Patient satisfaction	Spiolto Respimat treatment, <i>n</i> (%)	Inhaling from Respimat device, <i>n</i> (%)	Handling of Respimat device, <i>n</i> (%)
Very satisfied	31 (11.1)	47 (16.9)	57 (20.5)
Satisfied	111 (39.9)	119 (42.8)	121 (43.5)
Rather satisfied	98 (35.2)	83 (29.9)	70 (25.2)
Neither satisfied nor dissatisfied	29 (10.4)	23 (8.3)	19 (6.8)
Rather dissatisfied	5 (1.8)	2 (0.7)	4 (1.4)
Dissatisfied	0 (0)	1 (0.4)	5 (1.8)
Very dissatisfied	2 (0.7)	1 (0.4)	0 (0)
Questionnaire not completed	2 (0.7)	2 (0.7)	2 (0.7)

Regarding safety, the 6-week treatment with tiotropium/olodaterol FDC showed a favorable safety profile, with a modest incidence of adverse events.

Limitations

The present study is not without its limitations, mostly those inherent to any observational study. First, it is an uncontrolled study in a field-practice population. Moreover, it is important to point out that the PF-10 was not specifically developed for evaluating limitation in respiratory patients. Although this tool is widely used in daily practice to evaluate if a person perceives any limitation in his/her physical functioning [45], it can be considered only as a proxy to evaluate changes in physical function.

CONCLUSIONS

In this field-practice study on Italian patients with COPD treated with tiotropium/olodaterol FDC with a Respimat inhaler for approximately 6 weeks under routine care conditions, the self-reported physical functioning and the general condition of patients were improved, and a high level of global satisfaction was reported

regarding the treatment and use of the Respimat device. Both improvement and satisfaction were observed across all GOLD ABCD classification groups, showing the suitability of this device for different subpopulations of patients with COPD.

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Compliance with Ethics Guidelines. The study was approved by the local institutional Ethics Committee (Comitato Etico Regione Calabria Sezione Area Centro) and written informed consent was obtained from each participant. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. This study is registered with ClinicalTrials.gov (NCT03003494).

Data Availability. The datasets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

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