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# Symptom Improvement with BDP/FF/G Fixed Triple Inhalation Powder in Moderate to Severe COPD Patients Uncontrolled with Dual Therapies: A Non-Interventional, Open-Label, Single-Arm, Prospective Study (RESPONSE Slovenia)

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**ABSTRACT**

People living with COPD are frequently inadequately treated due to underdiagnosis or misdiagnosis. The aim of this study was to evaluate the real-world performance of the beclomethasone dipropionate/formoterol fumarate/glycopyrronium (BDP/FF/G) fixed triple combination formulated in a dry powder inhaler (DPI) in improving symptoms, lung function, and adherence in moderate to severe COPD patients uncontrolled on dual therapies. We conducted a non-interventional, open-label, single-arm, multicenter, prospective study across 19 outpatient centers in Slovenia. The primary objective was to measure symptom improvement with the COPD Assessment Tool (CAT). A total of 359 patients with moderate to severe COPD (97% classified as GOLD E, frequent exacerbators) were followed for 24 weeks. There was a significant 6-point reduction in the CAT score after switching from dual therapies to BDP/FF/G inhalation powder (95% CI: −7.0 to −5.5; $p<0.0001$). $FEV_1$ increased by 110 mL (95% CI: 90–130; $p<0.0001$) and FVC by 95 mL (95% CI: 65–120; $p<0.0001$), reaching a statistically significant improvement of 2.5 percentage points in the $FEV_1$/FVC quotient. The net improvement in dyspnea severity was 50.9% (95% CI 44.7%–57.2%), as assessed using the modified Medical Research Council (mMRC) Scale. Treatment adherence improved significantly after 6 months of triple therapy. In our cohort, switching uncontrolled moderate-to-severe COPD patients from dual therapy to BDP/FF/G fixed triple inhalation powder led to significant improvements in symptoms, lung function, dyspnea, sleep quality, and treatment adherence.

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Beclomethasone dipropionate/formoterol fumarate/glycopyrronium; COPD; COPD assessment tool (CAT); DPI; mMRC; NEXThaler®

## Introduction

People living with COPD are frequently inadequately treated due to underdiagnosis or misdiagnosis (1,2). Moreover, many patients do not seek care until symptoms become more limiting or acute exacerbations occur. Catching these symptoms early in the course of the disease could slow COPD progression and improve the quality of life of people living with COPD, thus having a major impact on public health.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of bronchodilators for patients with dyspnea and recommends the use of ICS-containing regimen only for patients

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with exacerbations (3). Several randomized controlled trials have shown that triple therapy combining inhaled corticosteroid (ICS), a long-acting $\beta_2$-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) is the most effective in reducing symptom burden (4–6). Since 2023 ICS/LABA are no longer recommended as a standalone maintenance therapy in COPD, instead endorsing ICS/LABA/LAMA as the preferred option when ICS use is indicated. This shift reflects the superior efficacy of triple therapies in improving lung function and symptom control, and reducing exacerbation rates (4–9).

The triple fixed combination of beclomethasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium (G) is approved in Europe for the treatment of COPD (Trimbow®, Chiesi Farmaceutici, Italy) (10). This triple combination was designed to produce extrafine particles of the active substances (i.e. with a mean mass median aerodynamic diameter [MMAD] < 2 µm), to optimize deposition throughout the bronchial tree, including the small airways (11). The safety and efficacy of BDP/FF/G delivered *via* pressurized metered-dose inhaler (pMDI) have been demonstrated in large randomized controlled trials and confirmed in real-world studies (5,6, 9,12–16). Collectively, these data show that BDP/FF/G is superior over LABA/LAMA, ICS/LABA, and LAMA monotherapy in reducing exacerbations and improving lung function, while remaining non-inferior to open triple therapy.

The fixed triple BDP/FF/G combination is also available as a dry powder inhaler (DPI; Trimbow® NEXTHaler), which retains extrafine particle delivery (17). The dry powder formulation matched the safety and efficacy of the pMDI version and outperformed ICS/LABA in the randomized, controlled TRI-D trial (17). However, real world studies evaluating the effectiveness and the uptake of BDP/FF/G inhalation powder in routine clinical settings remain limited (18). To fill this gap, the observational NEXThale**R** Real-world Study Assessing the **E**ffectiveness**S** of BDP/FF/G Fixed Tri**P**le C**O**mbi**N**ation on **S**ymptom Scor**E**s in COPD (RESPONSE) study was launched in four European countries to explore the real world performance of the fixed triple BDP/FF/G inhalation powder formulation in improving symptoms, quality of life, and lung function in moderate to severe COPD patients. Here, we report the findings from the Slovenian RESPONSE cohort, which included over 350 patients uncontrolled with dual ICS/LABA or LABA/LAMA combinations.

## Materials and methods

### *Study design and patient population*

The Slovenian arm of the RESPONSE study was a non-interventional, open-label, single-arm, multicenter, prospective study conducted in 19 outpatient centers to explore the real world performance of BDP/FF/G (88/5/9 µg) fixed triple inhalation powder (Trimbow® NEXThaler, Chiesi Farmaceutici, Parma, Italy) on symptom improvement in moderate to severe COPD patients, uncontrolled with inhaled dual therapies.

The study protocol was approved by the National Medical Ethics Committee of the Republic of Slovenia and complied with the European regulations on the performance of pharmacovigilance activities (EU520/2022, EC726/2004, and EC 2001/83). It was designed according to the Declaration of Helsinki (2013) and the International Conference on Harmonization of Good Clinical Practices (ICH-GCPs).

Patients were considered for inclusion after a pulmonologist had made a prior therapeutic decision regarding the study treatment. Inclusion criteria were age ≥ 35 years, outpatient, without any functional impairment, COPD diagnosis confirmed by a pulmonologist at least 1 year prior to study entry, spirometry conducted no more than 1 month before or on the day of study entry, and indication for treatment with Trimbow BDP/FF/G fixed triple inhalation powder (according to the summary of product characteristics10) no more than 1 week before or on the day of study inclusion. The treatment decision was independent of the patient's participation in this non-interventional trial. Additionally, patients had to be willing and capable of providing informed consent for the use of their pseudo-anonymized clinical data.

Patients were excluded if they had participated in any clinical trial within 30 days prior to inclusion, had a diagnosis of asthma (concurrently with COPD), had long-term use of oral corticosteroids, or had chronic home oxygen therapy. Those who had a severe exacerbation (requiring hospitalization)

within the last 4 weeks prior to inclusion were also excluded to ensure a stable baseline and reduce the effects of post-exacerbation recovery, which could influence symptoms and spirometry. Patients with other uncontrolled major respiratory or other organ system diseases that could significantly contribute to COPD symptoms (such as untreated heart failure, symptomatic anemia, etc.), those unable to complete the required questionnaires in the study, and those displaying any of the contra-indications listed in the BDP/FF/G (88/5/9 µg) SmPC were also excluded (10).

Patients were followed for 6 months. Data were collected at three visits: The first (baseline) visit was the inclusion visit, conducted as a routine follow-up in accordance with standard clinical practice. The second visit took place 1 month after the baseline visit (±3 days), and the third (final) visit took place 6 months after the baseline visit (±7 days).

The observational plan did not involve any study-specific procedures. Data collection was limited to information available in the patient's records as part of standard clinical practice in Slovenia. At all three visits, patients completed the COPD Assessment Test (CAT) and the Test of Adherence to Inhalers (TAI) questionnaires, and dyspnea was evaluated using the modified Medical Research Council (mMRC) scale. Lung function (spirometry) was assessed at least at the first (baseline) and third (final) visits according to the European Respiratory Society/American Thoracic Society spirometry technical standards (19). All patients received instruction on the proper use of the NEXThaler inhaler.

### Study endpoints

The primary objective of the study was to measure symptom improvement after switching from dual therapies to BDP/FF/G inhalation powder using the COPD Assessment Tool (CAT). The CAT questionnaire is a straightforward symptom assessment tool validated for routine use in clinical practice (20). It consists of eight questions, each scored on a 0–5 scale, assessing key symptoms such as cough, sputum production, chest tightness, breathlessness, activity limitations, confidence leaving home, sleep quality, and energy levels. The total score ranges from 0 to 40, with higher scores indicating worse symptom burden and health impact. Minimum clinically important difference (MCID) for CAT is considered to be a reduction in score of 2 or more points (21).

Secondary endpoints included changes in forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC), the proportion of patients with a CAT score improvement of ≥ 2 points, changes in cough occurrence, sputum production, and nocturnal symptom frequency, treatment adherence measured by the TAI score, and dyspnea severity assessed using the mMRC scale. The TAI questionnaire consists of 12 items, of which 10 are patient-reported (scored from 0–5), and two are healthcare provider-reported (i.e. inhaler technique assessment and dose adjustments, scored 0–2) (22). The mMRC is a simple grading system scoring the level of breathlessness during daily activities (0 = *No breathlessness except with strenuous exercise*, and 4 = *Too breathless to leave the house or breathless when dressing/undressing*). An mMRC ≥ 2 is considered clinically significant dyspnea (3). Adverse events were also recorded.

### Statistical analysis

All patients who met the entry criteria and attended all three scheduled visits were included in the statistical analysis. Numeric variables are presented as mean ± standard deviation (SD), and categorical variables as absolute numbers and percentages. The number of missing data points is reported where applicable.

No formal sample size calculation was performed, as no formal hypothesis was tested. Each patient contributed to the analysis with the available data. Statistical comparisons between Visit 1 and Visit 3 were conducted using the Wilcoxon paired-samples test. This non-parametric method provides the Hodges–Lehmann estimator (pseudo-median) as a measure of central tendency. Unlike the standard median, the Hodges–Lehmann estimator is calculated from all possible pairwise differences between observations, offering greater statistical precision.

A non-parametric permutation ANCOVA using the Freedman–Lane method was used to compare of the CAT outcome by prior therapy (ICS/LABA or LABA/LAMA), smoking status, and baseline

CAT score. Logistic regression was performed to assess the probability of achieving MCID based on CAT score, COPD duration, smoking status, severe and moderate exacerbations in the previous year, age, sex, and prior therapy. The final model was obtained by backward elimination of non-significant predictors ($p \geq 0.05$).

All statistical tests were conducted as exploratory analyses with $\alpha = 0.05$ and were not multiplicity controlled. All *P*-values are two-sided. Statistical analyses were conducted using R (version 4.4.1).

## Results

### *Study population and baseline characteristics*

Figure 1 illustrates the patient disposition in the Slovenian RESPONSE study. A total of 378 patients were recruited between May 9, 2023, and October 30, 2024. Of these, 19 were excluded from the analysis. Thus, the analysis included 359 patients. Prior treatment with LABA/LAMA (54%) was slightly more common than ICS/LABA (46%). Most patients (97.5%) were on stable maintenance therapy for ≥12 months prior to enrollment.

Most participants were male (59%), and the cohort's mean age was 68.4 years, with more than 65% aged 65 or older (Table 1). A smoking history was present in nearly all participants (>97%). Among them, 56% were current smokers with a mean smoking duration of 40 years, and 41% were former smokers with an average smoking duration of 33 years. The mean time since COPD diagnosis was 10.6 years, with the majority of participants classified as GOLD group E (97%).

Over 60% of participants had two or more comorbidities. The most common was arterial hypertension (56%), followed by hypercholesterolemia (39%) and gastroesophageal reflux (25%). Other comorbidities with a prevalence of ≥10% included benign prostatic hyperplasia, sleep disorders, diabetes, ischemic heart disease, and anxiety. The mean number of moderate and severe exacerbations in the previous 12 months was 1.7 and 1, respectively.

### *Symptom improvement assessed with the CAT questionnaire*

There was a significant improvement in the CAT score after switching from dual therapies to BDP/FF/G inhalation powder. The switch was associated with a significant reduction of −6 points (95% CI: −7.0 to −5.5; $p < 0.0001$) from the baseline visit (Visit 1) to the final visit (Visit 3, at 6 months, Figure 2A). Notably, improvements were observed across all CAT items (Figure 2B). From Visit 1 to Visit 3, 276 patients (77%) achieved an improvement of ≥2 points in the CAT score, meeting the MCID[21].

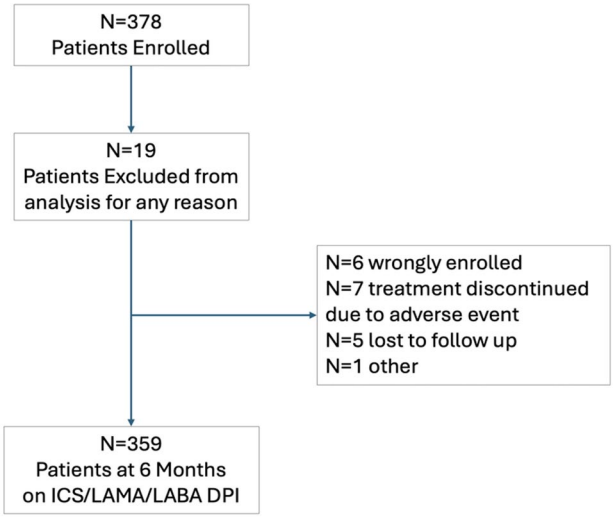


**Figure 1.** Patient disposition in the Slovenian RESPONSE study. DPI, dry-powder inhaler; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonists.

**Table 1.** Baseline characteristics by pre-study inhalation therapy.

| | Pre-study inhalation therapy | | All |
|---|---|---|---|
| Baseline characteristics | ICS-LABA (*N* = 165) | LABA-LAMA (*N* = 194) | Full cohort (*N* = 359) |
| Age (years), mean (SD) | 68.4 (9.3) | 68.4 (8.6) | 68.4 (8.9) |
| Age group, *N* (%) | | | |
| <65 years, *N* (%) | 53 (32.1%) | 63 (32.5%) | 116 (32.3%) |
| ≥65 years, *N* (%) | 112 (67.9%) | 131 (67.5%) | 243 (67.7%) |
| Sex, *N* (%) | | | |
| Male | 94 (57.0%) | 118 (60.8%) | 212 (59.1%) |
| Female | 71 (43.0%) | 76 (39.2%) | 147 (40.9%) |
| Number of comorbidities, *N* (%) | | | |
| 0 | 27 (16.4%) | 36 (18.6%) | 63(17.5%) |
| 1 | 43 (26.1%) | 30 (15.5%) | 73 (20.3%) |
| 2 | 36 (21.8%) | 48 (24.7%) | 84 (23.4%) |
| 3 | 20 (12.1%) | 33 (17.0%) | 53 (14.8%) |
| ≥4 | 39 (23.6%) | 47 (24.2%) | 86 (24%) |
| Main comorbidities (≥10% incidence), *N* (%) | | | |
| Arterial hypertension | 93 (56.4%) | 108 (55.7%) | 201 (56%) |
| Hypercholesterolemia | 63 (38.2%) | 76 (39.2%) | 139 (38.7%) |
| Gastroesophageal reflux | 50 (30.3%) | 41 (21.1%) | 91 (25.3%) |
| Benign prostatic hyperplasia | 23 (13.9%) | 30 (15.5%) | 53 (14.8%) |
| Insomnia/other sleep disorders | 12 (7.3%) | 30 (15.5%) | 42 (11.7%) |
| Diabetes | 24 (14.5%) | 14 (7.2%) | 38 (10.6%) |
| Ischemic heart disease | 17 (10.3%) | 20 (10.3%) | 38 (10.6%) |
| Anxiety | 12 (7.3%) | 24 (12.4%) | 36 (10%) |
| Smoking status, *N* (%) | | | |
| Current smoker | 83 (50.3%) | 118 (60.8%) | 201 (56%) |
| Ex-smoker | 74 (44.8%) | 74 (38.1%) | 148 (41.2%) |
| Never smoked | 8 (4.8%) | 2 (1.0%) | 10 (2.8%) |
| Smoking duration (years), mean (SD) | | | |
| Active smokers | 37.3 (11.3) | 41.6 (11.4) | 40 (11.5) |
| Former smokers | 33.0 (11.2) | 33.6 (10.9) | 33 (11) |
| Pack-years, mean (SD) | | | |
| Current smokers | 34.3 (16.5) | 36.7 (19.0) | 36 (18) |
| Former smokers | 36.8 (18.1) | 41.2 (21.9) | 39 (20) |
| Time since COPD diagnosis (years), mean (SD)* | 11.3 (6.5) | 9.0 (6.0) | 10.6 (6) |
| GOLD group, *N* (%) | | | |
| A | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| B | 5 (3.0%) | 7 (3.6%) | 12 (3.3%) |
| E | 160 (97.0%) | 187 (96.4%) | 347 (96.6%) |
| Previous treatment duration, | | | |
| ≥12 months | – | – | 350 (97.5%) |
| <12 months | – | – | 9 (2.5%) |
| CAT score, mean (SD) | 24.5 (6.8) | 24.0 (6.5) | 24.2 (6.6) |
| $FEV_1$%, mean (SD) | 53.3 (12.0) | 52.2 (12.8) | 53 (12) |
| $FEV_1$ (L), mean (SD) | 1.44 (0.44) | 1.41 (0.45) | 1.43 (0.45) |
| FVC (L), mean (SD) | 2.59 (0.71) | 2.59 (0.76) | 2.59 (0.73) |
| $FEV_1$/FVC (%), mean (SD) | 56.0 (8.6) | 54.8 (8.9) | 55 (9) |
| No. of participants with pulmonary exacerbations (previous 12 months), *n* (%) | | | |
| Moderate | | | |
| 0 | 17 (10.3%) | 19 (9.8%) | 36 (10%) |
| 1 | 54 (32.7%) | 55 (28.4%) | 109 (30.4%) |
| 2 | 81 (49.1%) | 111 (57.2%) | 192 (53.5%) |
| ≥3 | 13 (7.9%) | 9 (4.6%) | 22 (6.1%) |
| Severe | | | |
| 0 | 65 (39.4%) | 68 (35.1%) | 133 (37%) |
| 1 | 56 (33.9%) | 75 (38.7%) | 131 (36.5%) |
| 2 | 30 (18.2%) | 37 (19.1%) | 67 (18.7%) |
| ≥3 | 14 (8.5%) | 14 (7.2%) | 28 (7.8%) |

**Abbreviations:** CAT, COPD Assessment Test; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, Inhaled Corticosteroids; LABA, Long-acting $Beta_2$ Agonist; LAMA, Long-acting Muscarinic Antagonists; $FEV_1$, Forced Expiratory Volume in the first 1 s; FVC, Forced Vital Capacity; SD, Standard deviation; SMD, Standardized Mean Difference.
*Time from diagnosis missing in *N* = 45 participants.

*Post hoc* analysis showed that CAT improvement was independent of prior therapy (LABA/LAMA or ICS/LABA; $p = 0.24$). In contrast, baseline CAT score ($p < 0.001$) and smoking status ($p = 0.003$) were significant predictors of the degree of improvement. Logistic regression was fitted for exploratory identification of baseline characteristics associated with achieving MCID. The variables (predictors) included in the full initial model, and their coefficients, are reported in Table 2. After elimination of non-significant predictors, the final model included baseline CAT, smoking status and COPD

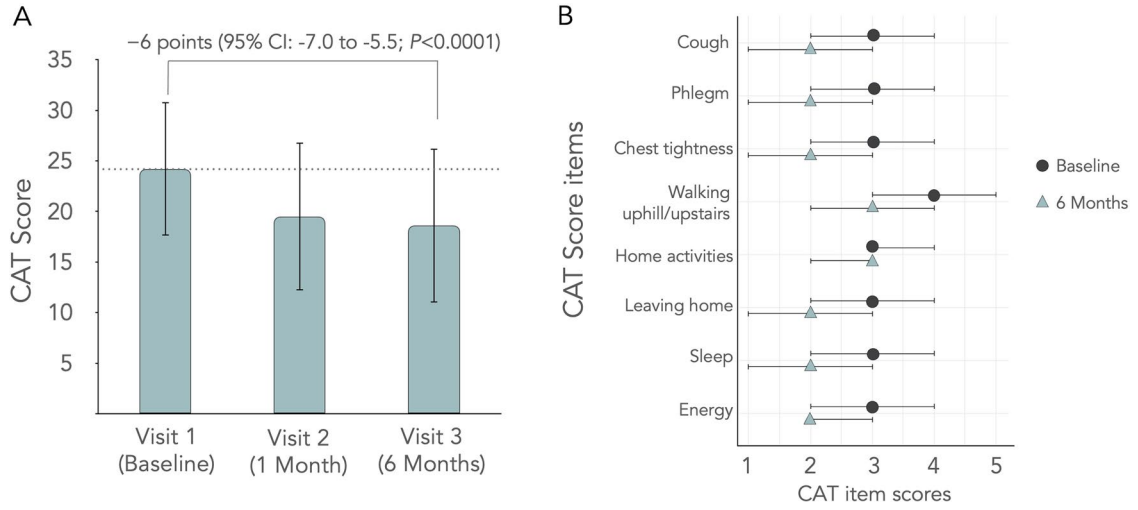


**Figure 2.** (A) COPD assessment tool (CAT) scores obtained at baseline (i.e. at treatment scalation from dual therapies [ICS/LABA or LABA/LAMA]), and after 1 and 6 months (Mo) on BDP/FF/G fixed triple inhalation powder. The dotted line indicates the mean CAT score at baseline. Data are presented as mean ± SD; Wilcoxon paired-samples test. (B) CAT items scores at baseline and after 6 months. Scores are shown with medians and interquartile ranges.

**Table 2.** The full multivariable model as fitted for the exploratory analysis of achieving CAT MCID.

| Predictor | Or | 95% CI | *p* |
|---|---|---|---|
| Baseline CAT score (per 1 point) | 1.10 | (1.05, 1.16) | <0.001 |
| COPD duration (per year) | 0.95 | (0.90, 0.99) | 0.033 |
| Smoking status: active (vs. former/never) | 0.48 | (0.26, 0.86) | 0.016 |
| Moderate exacerbations in previous year (per event) | 1.13 | (0.72, 1.76) | 0.604 |
| Severe exacerbations in previous year (per event) | 1.21 | (0.84, 1.79) | 0.325 |
| Age (per year) | 1.00 | (0.97, 1.03) | 0.999 |
| Prior inhalation therapy: LABA/LAMA (vs. ICS/LABA) | 0.98 | (0.55, 1.73) | 0.934 |
| Sex: male (vs. female) | 1.12 | (0.63, 1.97) | 0.704 |

**Abbreviations:** CAT, COPD Assessment Test; COPD, Chronic Obstructive Pulmonary Disease; ICS, Inhaled Corticosteroids; LABA, Long-acting Beta$_2$ Agonist; LAMA, Long-acting Muscarinic Antagonists.

**Table 3.** Spirometry outcomes.

| | Visit 1 (baseline) | Visit 2[a] (1 month) | Visit 3 (6 months) | Difference visit 1–visit 3[b] (95% CI) | *p*-value[c] |
|---|---|---|---|---|---|
| $FEV_1$, L mean [SD] | 1.43 (0.45) | 1.64 (0.57) | 1.55 (0.55) | 0.11 (0.09–0.13) | <0.0001 |
| $FEV_1$ %, mean [SD] | 53% (12) | 59% (16) | 57% (15) | 4 (3.5–5) | <0.0001 |
| FVC, L mean (SD) | 2.59 (0.73) | 2.82 (0.80) | 2.67 (0.77) | 0.095 (0.065–0.12) | <0.0001 |
| $FEV_1$/FVC | 55 (9) | 58 (10) | 58 (10) | 2.5 (2.0–3.0) | <0.0001 |

[a]Visit 2 (1 month) data should be interpreted with caution due to 153 missing observations.
[b]Hodges-Lehmann estimator.
[c]Wilcoxon paired-samples test.
$FEV_1$, Forced Expiratory Volume at 1 s; $FEV_1$ %, $FEV_1$ Percentage Predicted; FVC, Forced Vital Capacity.

duration. Each additional baseline CAT point was associated with a 10% increase in the odds of achieving MCID (odds ratio [OR] 1.10, 95% CI 1.05–1.16, $p < 0.0001$). Active smokers had 52% lower odds of achieving MCID than non-smokers/former smokers (OR 0.48, 95% CI 0.26–0.86, $p = 0.041$). Each additional year of COPD duration was associated with a 4% decrease in the odds (OR 0.96, 95% CI 0.92–1.00, $p = 0.016$).

## *Spirometry outcomes*

Between Visit 1 and Visit 3, the mean change in $FEV_1$ was 110 mL (95% CI: 90–130; $p < 0.0001$). The corresponding increase in percent predicted $FEV_1$ was 4% (95% CI: 3.5–5.0; $p < 0.0001$) (Table 3). An improvement in $FEV_1$ of ≥100 mL was observed in 168 patients (46.8%), while an increase of ≥10

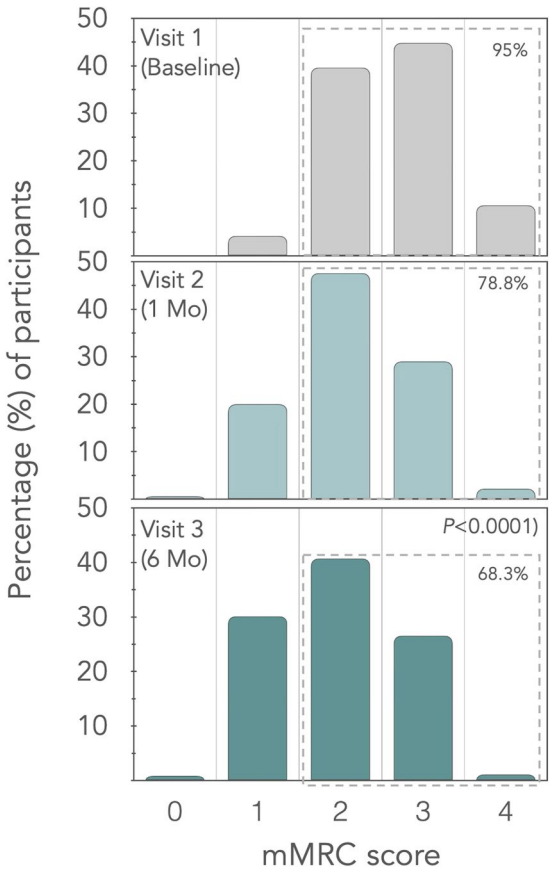


**Figure 3.** Distribution of dyspnea severity in RESPONSE participants, assessed using the Modified Medical Research Council Dyspnea Scale(mMRC) at baseline (visit 1, i.e. at treatment scalation from dual therapies [ICS/LABA] or LABA/LAMA]), after 1 month (visit 2), and after 6 months (visit 3).

percentage points in percent predicted $FEV_1$ was observed in 77 patients (21.5%). Forced vital capacity (FVC) increased by 95 mL (95% CI: 65–120; $p < 0.0001$), with 167 patients (46.5%) demonstrating an improvement of ≥100 mL. A statistically significant improvement of 2.5 percentage points was also found in the $FEV_1$/FVC quotient (95% CI: 2.0–3.0, $p < 0.0001$).

### *Dyspnea: mMRC scores*

The change in the distribution of mMRC scores from Visit 1 to 3 was significantly reduced after 6 months of treatment with BDP/FF/G DPI ($p < 0.0001$, Stuart-Maxwell test) (Figure 3). Overall, the score improved in 198 patients, remained unchanged in 137, and worsened in 18 patients (data of $N = 6$ participants missing). The proportion of participants with mMRC score ≥ 2 was reduced from 95% at baseline to 68% after 6 months of triple DPI treatment. The net mMRC score improvement (the proportion of patients with improvement minus the proportion of patients with deterioration) was 50.9% (95% CI 44.7%–57.2%).

### *Cough occurrence, sputum production, and nocturnal symptoms*

Cough occurrence, sputum production, and nocturnal symptoms improved significantly after switching from dual therapies to BDP/FF/G inhalation powder. Improvements in cough were 2.7 times more frequent than deteriorations (paired OR: 2.72; 95% CI: 1.67–4.44). Among the 281 participants who reported cough at baseline, 60 no longer reported this symptom after 6 months of treatment ($p < 0.0001$, McNemar test) (Figure 4A). Similarly, improvements in sputum production were 3.2 times more

frequent than deteriorations (paired OR: 3.15; 95% CI: 2.00–4.90). Of the 241 patients who reported sputum production at baseline, 82 no longer reported it at Visit 3.

The distribution of the occurrence of nocturnal symptoms significantly improved 6 months after switching to the fixed triple inhalation powder therapy ($p < 0.0001$, Stuart-Maxwell test) (Figure 4B). The number of participants without nocturnal symptoms increased by almost 50% after 6 months. Overall, 108 participants (30.1%) improved, 185 (51.5%) remained unchanged, and 66 (18.4%) worsened. The net improvement rate, calculated as the proportion of patients with improvement minus the proportion of patients with deterioration, was 11.7% (95% CI: 4.4%–18.9%).

### *TAI questionnaire outcomes*

The mean TAI score increased from 47 ± 6.6 at baseline, with their previous dual therapy, to 49 ± 6.3 after 6 months on BDP/FF/G inhalation powder. ($p < 0.0001$). The Wilcoxon paired-samples test demonstrated a statistically significant improvement in TAI score by 3 points from baseline to visit 3 (95% CI: 2.0–3.5; V 7,841, $p < 0.0001$) (Table 4).

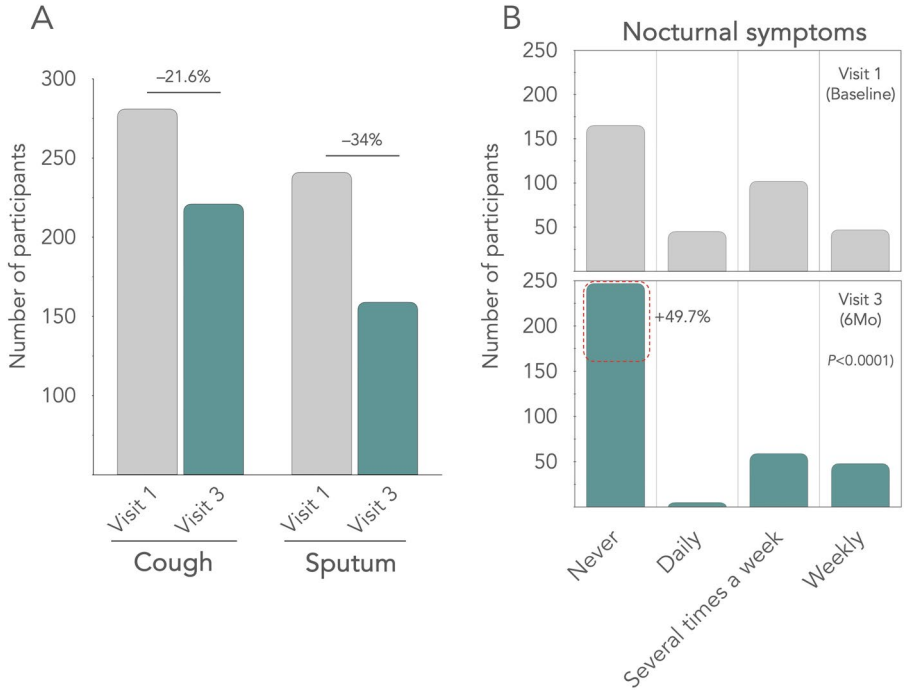


**Figure 4.** (A) Number of participants reporting cough and sputum production at baseline (Visit 1, i.e. at treatment scalation from dual therapies [ICS/LABA] or LABA/LAMA]) and after 6 months on BDP/FF/G fixed triple inhalation powder (Visit 3). (B) Changes in the distribution of the number of RESPONSE participants reporting nocturnal symptoms at baseline (visit 1) and after 6 months (visit 3). Significant reductions in the number of participants reporting cough and sputum production were found ($p < 0.0001$, McNemar test). The Stuart–Maxwell test was used to evaluate changes in the distribution of participants reporting nocturnal symptoms between visit 1 and visit 3.

**Table 4.** Test of adherence to inhalers (TAI) questionnaire outcomes.

| | Visit 1 (baseline) | Visit 3 (6 months) |
|---|---|---|
| TAI score, mean (SD) | 47 (6.6) | 49 (6.3)*** |
| Adherence categories, *n* (%) | | |
| Poor | 206 (57.4%) | 131 (36.5%) |
| Intermediate | 45 (12.5%) | 59 (16.4%) |
| Good | 108 (30.1%) | 169 (47.1%) |

***$p < 0.0001$, Wilcoxon paired-samples test.
Adherence was categorized as good (TAI score 50), intermediate (TAI 46–49), or poor (TAI ≤ 45).
TAI, Test of Adherence to Inhalers.

Based on patient responses to the first 10 TAI items, adherence was categorized as good (score 50), intermediate (46–49), or poor (≤ 45). Of the 206 participants with "poor adherence" at the baseline visit, adherence remained unchanged in 119 patients until Visit 3, improved to "intermediate" in 35 patients, and improved to "good" in 52. Notably, the proportion of participants with poor adherence decreased by 36%, while the proportion with good adherence increased by 56%. The distribution of adherence categories from baseline to visit three was statistically significant ($p < 0.0001$, Stuart-Maxwell test).

### Exacerbations

During the follow-up, there were 236 moderate and 109 severe exacerbations. Proportions of patients reporting any number of moderate exacerbations were 29.2% (1 event), 16.2% (two events) and 1.4% (3 events). Proportions for severe exacerbations were 17.3% (1 event), 5.3% (two events) and 0.8% (3 events). The follow-up period was limited to 24 weeks, so no further analysis of this outcome was possible.

### Adverse events

Adverse effects occurred in seven patients. In six cases, the adverse events were not serious (cough, cramps, insomnia, lack of drug effect, discomfort, dry mouth, tremor, and dizziness) while 1 adverse event was serious (cerebrovascular accident), but unrelated to the study drug. No pneumonias or deaths were registered during the follow-up.

## Discussion

The Slovenian arm of the RESPONSE study shows that switching moderate to severe COPD patients uncontrolled on dual therapies to the fixed triple BDP/FF/G inhalation powder combination leads to improvements in symptoms and other respiratory outcomes. Importantly, as 97% of enrolled patients were classified as GOLD Group E (i.e. exacerbators), this therapeutic escalation was fully consistent with current GOLD recommendations (3). Switching to the fixed triple therapy significantly improved overall symptom burden, as reflected by lower CAT scores. Patients experienced less dyspnea, cough, sputum production, and nocturnal discomfort, together with improved lung function and better adherence to treatment, while improving lung function and treatment adherence in a substantial proportion of participants.

The safety and efficacy of fixed BDP/FF/G combination have been demonstrated in three European trials (TRILOGY, TRINITY, and TRIBUTE) (5,6,9), and in one trial conducted in an East Asian population (TRIVERSYTI) (12), showing significant improvements in lung function and reductions in exacerbations compared with ICS/LABA, LABA/LAMA, and LAMA monotherapy, while demonstrating non-inferiority to open triple therapy. European observational studies have further confirmed these lung function benefits in the real world, reporting in addition significant symptom reduction in patients uncontrolled on dual therapies (LABA/LAMA or ICS/LABA) and even in those previously treated with open triple combinations (ICS/LABA + LAMA) (13–16). While all these studies were conducted using pMDIs for BDP/FF/G delivery, the formulation is also available as a DPI (17).

The BDP/FF/G fixed triple inhalation powder is delivered with the NEXThaler, which retains the extrafine particle generation and releases BDP/FF/G aerosols upon the exertion of an inspiratory flow rate of 35 L/min (23). The TRI-D trial demonstrated that the fixed triple combination delivered *via* the NEXThaler® DPI was non-inferior to the pMDI formulation. Moreover, the DPI formulation showed superiority over ICS/LABA in enhancing lung function and reducing exacerbations (17). Providing the same drug formulation in both pMDI and DPI formats offers advantages for patients and prescribing physicians. It allows patient-centered device selection based on inspiratory flow and coordination skills, ensures therapeutic continuity when switching devices, supports adherence by matching patient preferences and technique, and simplifies prescribing and training.

The RESPONSE observational study was initiated in four European countries to evaluate the real-world effectiveness of BDP/FF/G inhalation powder in improving symptoms, quality of life, and

lung function in moderate to severe COPD patients uncontrolled with dual therapies. Recently, the Hungarian arm of RESPONSE reported a significant reduction of the CAT score over 6 months from 20.5 to 14.2 and a significant improvement in lung function ($FEV_1$ increase from 1.33 to 1.45 L) (18), consistent with the mean 6-point reduction in CAT score and the $FEV_1$ improvement of 0.11 L observed in our cohort. Moreover, 77% of participants in our cohort achieved $a \geq 2$ point reduction in the CAT score, meeting the threshold for the MCID (21). The improvement in CAT scores was independent of prior dual therapy (ICS/LABA or LABA/LAMA), suggesting that individuals uncontrolled on bronchodilators may benefit from the addition of ICS. However, symptom improvement was attenuated in active smokers, thus emphasizing the importance of smoking cessation. Switching to BDP/FF/G inhalation powder also improved dyspnea significantly, with the proportion of patients reporting substantial breathlessness (i.e. mMRC score ≥2) decreasing from 95% at baseline to 68% after six months of treatment.

The results of the Slovenian arm of RESPONSE should be interpreted in the context of the cohort's baseline characteristics relative to other real-world studies evaluating the effectiveness of the BDP/FF/G fixed triple combination (13–16). In the Slovenian cohort, 68% of participants were aged 65 years or older, and more than 60% had 2 or more comorbidities. The cohort also presented the highest mean baseline CAT score across studies (24.2 points vs. 21.5 in the German and Greek studies) (13,15), the longest mean disease duration (10.6 years vs. 7–8 years in other real-world studies) (13–16), and the largest proportion of GOLD group E patients at baseline (97% vs. <35% in the Austrian and German cohorts) (13,14). Interestingly, despite these markers of higher disease burden, the present cohort showed less airflow limitation ($FEV_1$ 53%) than other real-world studies (43%–51%) and the pivotal trials (36%) (5,6, 9,13–16). The consistent symptom improvement observed with the fixed triple BDP/FF/G combination in uncontrolled patients across heterogeneous European cohorts highlights the benefits of switching to triple therapy in diverse COPD patient populations. Collectively, these findings align with the GOLD recommendation to initiate triple therapy earlier in the course of the disease when an ICS is indicated (3), while also prompting questions about the optimal timing for initiating triple therapies in symptomatic patients inadequately controlled with mono- or dual-bronchodilator regimens. Nevertheless, the benefits of escalating to triple therapies depend on careful patient selection and must be weighed against its potential risks, including an increased risk of pneumonia and other ICS-related adverse events.

Switching from dual therapies to BDP/FF/G inhalation powder significantly improved cough, sputum production, and nocturnal symptoms in a substantial proportion of participants, with cough and sputum reductions likely reflecting greater benefits in those with marked chronic bronchitis phenotype. The proportion of patients without nocturnal symptoms increased by nearly 50% after 6 months of treatment, and one-third reported better sleep quality. In COPD, nocturnal hypoventilation, altered respiratory mechanics, and comorbidities such as obstructive sleep apnea contribute to poor sleep quality, frequent awakenings, and increased nighttime dyspnea (24). These factors worsen daytime symptoms, impair quality of life, and increase the risk of exacerbations and mortality. Furthermore, epidemiological studies have linked poor sleep quality to hypertension, coronary heart disease, and diabetes mellitus (25), a set of comorbidities observed in the Slovenian RESPONSE cohort and of significant prevalence in the broader COPD population.

Adherence to inhaled therapy is essential for achieving disease control, reducing exacerbation rates, and improving quality of life in patients with COPD (26). However, non-adherence remains a common and significant barrier to treatment effectiveness (27). In the present study, 57% of participants reported poor adherence at baseline, while on dual therapies, in line with previous studies reporting poor adherence in 30%–60% of COPD patients across different populations and periods (28–32). Although about half of the patients with poor baseline adherence remained non-adherent after six months, over 40% showed substantial improvement. Key determinants of adherence include patient-related factors, inhaler complexity, and training in the inhaler technique (27). While simpler, more intuitive inhalers can improve adherence, devices requiring complex coordination can hinder it. The NEXThaler features a dose counter and a breath-actuated mechanism that facilitates inhalation of extrafine particles. In a study enrolling 72 COPD patients across all GOLD stages, all participants

were able to generate sufficient inspiratory flow to activate the NEXThaler's breath-actuated mechanism, achieving consistent performance and usability regardless of their airflow limitation (33). In the present study, the switch visit included structured inhaler training, which likely contributed to improve technique and adherence. In addition, symptoms improvement may have further reinforced regular use in this highly symptomatic cohort (34).

The present study has several limitations, including the absence of a comparator arm and the 6-month follow-up period, which limits conclusions about the long-term benefits of the switch and precludes assessment of its effect on the annualized rate of exacerbations. Importantly, patients were not re-trained in the inhaler use before the switch, so the extent of re-training effect could not be evaluated in this study. Finally, blood eosinophil counts were not systematically collected in the study as eosinophil counts are not routinely required to escalate to triple therapies in Slovenia, so we could not evaluate this parameter as a response predictor.

## Conclusion

The Slovenian arm of the RESPONSE study demonstrates that switching moderate-to-severe COPD patients who remain uncontrolled on dual therapies to the fixed BDP/FF/G inhalation powder combination results in significant improvements in CAT scores, lung function, dyspnea, and treatment adherence. Additionally, substantial reductions in cough, sputum production, and nocturnal symptoms were observed. These benefits were observed in a cohort of frequent exacerbators (97% were GOLD E) with a high baseline symptom burden and multiple comorbidities, and are consistent with both pivotal trials and European real-world studies.

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## Author contributions

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## Data availability statement

Data are available from the corresponding author upon reasonable request, subject to applicable ethical and privacy considerations.

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