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Original Research

Real-world efficacy of BDP/FF/G fixed triple inhalation powder (NEXThaler) therapy in the treatment of moderate to severe COPD patients (RESPONSE study)

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) remains a leading cause of morbidity and mortality worldwide, placing a significant burden on healthcare systems and patients' quality of life. The cornerstone of treatment includes fixed triple combinations of inhaled corticosteroids (ICS), long-acting β2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) shown to improve lung function, reduce exacerbations, and enhance symptom control in patients with moderate to severe disease. However, there is still a lack of clinical evidence for the real-life effectiveness of fixed triple combinations.

Patients and methods: RESPONSE was a non-interventional, prospective, 26-week study, assessing the effectiveness of beclometasone/formoterol/glycopyrronium-bromide (BDP/FF/G) 88/5/9 μg administered via a dry powder inhaler (DPI), in symptomatic COPD patients, with moderate to severe airflow obstruction, previously treated with LABA-LAMA or ICS-LABA dual combinations. The study included 3 visits, where data on demographic and COPD-specific parameters, symptoms, quality of life (based on the EQ-5D-3L questionnaire), adherence (based on the TAI-12 questionnaire) and lung function were collected. The primary objective was the change of COPD Assessment Test (CAT) scores during the study, compared to baseline.

Results: Altogether, data of 1336 patients had been analysed. Their average age was 67 years and 50.3 % were female. The average CAT score was 20.4 and the average FEV_1 was 52.3 %. Most patients had some limitation in one or more dimensions of EQ-5D-3L, with an average visual analogue scale score (VAS) of 59.1. After 6 months of treatment, there was a significant and clinically relevant improvement in average CAT score by 6.3 points (95 % CI: 6.0–6.7; $p < 0.001$) and average FEV_1 by +120 mL (95 % CI: 100–140, $p < 0.001$). There was a significant improvement in all dimensions of EQ-5D-3L, with an average increase of 12.1 (95 % CI: 11.3–12.3, $p < 0.001$) points in the VAS score.

Conclusion: The RESPONSE study is the first to evaluate the real-world effectiveness of the BDP/FF/G 88/5/9 μg DPI in patients with moderate to severe COPD. At the time of publication, this DPI formulation represents the only available extrafine particle-size fixed triple combination therapy for COPD. We demonstrated that BDP/FF/G DPI led to improvements in symptoms, quality of life, lung function, and even in adherence after patients were switched from dual therapy (LABA/LAMA or ICS/LABA).

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and debilitating respiratory condition, ranking as the fourth leading cause of death worldwide, responsible for approximately 3.5 million lives lost in 2021, accounting for about 5 % of all global deaths [1].

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COPD is a progressive disease characterized by persistent respiratory symptoms like exertional dyspnea, chronic cough, and excessive mucus, significantly impacting daily life. Over time, lung function declines despite treatment, leading to progressive worsening of physical activity and medical dependence. Acute exacerbations, often triggered by infections or pollutants, worsen symptoms, accelerate progression, and raise hospitalization risks, highlighting the need for effective management.

The primary objectives of maintenance therapy for COPD include symptom control, improvement of exercise tolerance, and exacerbation prevention [2]. Achieving these objectives requires a comprehensive approach that includes both pharmacologic interventions, such as bronchodilators (*Long-Acting Beta2-Agonists* – LABA; *Long-Acting Muscarinic Antagonists* – LAMA) and inhaled corticosteroids (ICS), as well as non-pharmacologic strategies like smoking cessation, vaccination, pulmonary rehabilitation, and patient education.

In COPD, disease stability refers to a state or period during which the patient's symptoms, lung function, and general health status remain relatively unchanged, with no acute exacerbations. Monitoring these characteristics together represents a new approach to COPD management which traditionally only assesses a single outcome. A recent review highlights key factors in defining disease stability as a universal treatment goal for all COPD patients, regardless of disease severity, phenotype, or treatment [3]. As proposed by the authors, disease stability can be established based on existing COPD components such as clinical control and deterioration, incorporating exacerbations, health status, and lung function.

Fixed triple combinations currently represent the mainstay of anti-inflammatory inhaled treatment for COPD as outlined in the GOLD 2025 guideline [2]. These combinations are typically recommended when managing frequent exacerbator COPD patients offering a comprehensive approach to symptom control and exacerbation prevention.

Over recent decades, a range of inhalation devices has been developed to enhance pulmonary drug delivery and improve clinical outcomes. Pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) remain the most widely used devices, offering distinct delivery mechanisms suited to varying levels of lung function and inspiratory capacity. This diversity facilitates individualized treatment approaches. Despite the availability of multiple inhaler types, current clinical guidelines provide no specific recommendations on optimal device–drug combinations. Consequently, inhaler selection is largely determined by patient characteristics and clinician preference. As therapeutic efficacy depends not only on the pharmacological properties of the drug but also on correct inhaler technique, appropriate device choice is critical.

A joint European Respiratory Society (ERS) and International Society for Aerosols in Medicine (ISAM) Task Force also highlighted that, although different aerosol systems can achieve comparable therapeutic effects when used correctly, patient technique and adherence are key determinants of success. Clinicians are therefore advised to base device choice on individual capability, provide structured instruction, and regularly reassess technique to ensure sustained efficacy [4,5].

As emphasized by *Scichilone* et al., device selection should consider inspiratory capacity, coordination, and overall clinical condition to ensure compatibility with the device's operational requirements [6]. Recent comparative data further underscore the importance of a personalized approach. In a study comparing Foster® NEXThaler® and Relvar® Ellipta®, lung dose deposition was influenced by breathing pattern, age, gender, and disease severity. Foster® NEXThaler® achieved higher deposition in approximately 85 % of participants, with inhalation flow, inspired volume, and breath-hold duration identified as key determinants of efficacy. These findings reinforce the need to tailor inhaler selection to patient-specific characteristics as a central component of COPD management [7].

Currently there are three inhaled triple combinations available. Furthermore, extrafine fixed-dose triple therapy containing beclometasone dipropionate (ICS), formoterol fumarate (LABA), and glycopyrronium (LAMA) (BDP/FF/G) is available delivered via a pMDI or a DPI device (NEXThaler). Due to its earlier marketing authorization an increasing number of real-world evidence studies supports the efficacy of BDP/FF/G pMDI in COPD: TRICOP [8] (Austria), TRIOPTIMIZE [9] (Germany), TRIBUNE [10] (Greece), TRIVOLVE [11] (Belgium), TRI-TRIAL [12] (Italy), TRIWIN [13] (Greece), and RATIONALE [14] (Hungary). However, real-world clinical data on the effectiveness of BDP/FF/G 88/5/9 μg DPI remain limited. While the noninferiority TRI-D [15] randomized controlled trial demonstrated that both formulations (pMDI and DPI) are effective in COPD – offering flexibility in inhaler selection based on patient preference and clinical parameters – real-world evidence supporting this finding is still lacking. To bridge this gap, the RESPONSE study was designed to be the first-ever real-world study evaluating the clinical efficacy of BDP/FF/G 88/5/9 μg DPI in moderate-to-severe COPD patients.

2. Material and methods

RESPONSE was a non-interventional, multicentre, prospective study to assess the efficacy of extrafine BDP/FF/G 88/5/9 μg DPI in everyday clinical practice after its use was initiated by a pulmonology specialist. Switching to therapy must have occurred no more than one week prior to study enrolment and must have been made based on the physicians' decision and independently of study participation, as part of routine care in accordance with the current Summary of Product Characteristics and with the Hungarian national treatment guidelines for escalation of COPD maintenance therapy in symptomatic COPD patients. In consequence, patient enrolment was permitted only after a therapeutic decision had been made by a pulmonology specialist. Given the non-interventional design of the study, no additional diagnostic procedures were required from investigators beyond standard clinical practice. Patients were withdrawn from the study if, during the observation period, their maintenance therapy was changed, and they were no longer receiving BDP/FF/G 88/5/9 μg DPI.

Similar study protocols were adopted in Slovenia, Bulgaria and Czech Republic for the local routine clinical practice. Herein we report the results of the Hungarian study. The study was uploaded to ClinTrials.gov under the unique identifier: NCT05743608.

2.1. Patients and procedures

2.1.1. Patient eligibility and study design

Patients were eligible for inclusion if they met the following criteria: a confirmed diagnosis of COPD by a specialist, established at least one year prior to enrolment; age ≥35 years; availability of spirometry results from the day of enrolment or within the preceding 30 days; presence of moderate to severe airflow limitation, defined as a post-bronchodilator forced expiratory volume in 1 s (FEV_1) between 30 % and 80 % of the predicted value. Even though ERS/ATS guidance [16] recommends the use of Z-scores for diagnosis of COPD, this approach is currently (and during the study was) not adapted to the Hungarian national guidelines for COPD diagnosis and treatment [17]. Indication for fixed triple therapy with BDP/FF/G 88/5/9 μg DPI, in accordance with the approved Summary of Product Characteristics; inadequate disease control on a fixed dual combination therapy (either LABA/LAMA or ICS/LABA), defined as ≥2 moderate and/or ≥1 severe COPD exacerbations in the 12 months prior to enrolment and symptomatic disease, evidenced by a CAT score ≥10 and/or a mMRC dyspnea score ≥2. Exacerbations were defined as acute worsening of COPD symptoms, which required the use of oral corticosteroids and/or antibiotics in outpatient setting (moderate) or required emergency department care or hospital admission (severe).

2.1.2. Study procedures and follow-up

Eligible patients were followed for a period of six months. Baseline data were collected at Visit 1 (V1). Follow-up assessments were conducted at 1 month (V2) and 6 months (V3) post-enrolment. At both follow-up visits, data collection included COPD-specific assessments, cough and sputum symptoms, Euro Quality of Life questionnaire (EQ-5D-3L), Test of Adherence to Inhalers-12 item (TAI-12), and inhalation technique. Lung function and laboratory values were recorded at V3 only if available (lung function: on the day of V3; laboratory: at any time during the study period), regardless of the study. Safety data (including all off-label usages) were documented at each visit, including.

2.1.3. Questionnaires

The EQ-5D-3L questionnaire assesses five dimensions of life quality (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) at three levels (no problems, some problems, and extreme problems). Additionally, during questionnaire completion, patients must evaluate their subjective life quality on a 0–100 VAS.

Treatment adherence was assessed using the TAI-12. This validated [18] questionnaire was developed in 2016 by experts from the integrated research programs on asthma and COPD of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). The first validated Hungarian-language version was completed in 2021. It is applicable for use in both asthma and COPD. Currently, it is the only questionnaire specifically designed to measure adherence related to inhaler use. When the aim is not only to assess the level of adherence but also to identify the type of non-adherence, the extended 12-item version of the TAI—featuring two additional items to be answered by a physician or healthcare assistant—is recommended. This version enables the differentiation of non-adherence patterns as follows: sporadic (occasional) non-adherence (total score of items 1–5<25 points); deliberate non-adherence (total score of items 6–10 < 25 points); unconscious (unintentional) non-adherence (items 11–12 score <4 points).

Currently, there is no universally accepted clinical metric for assessing the severity of cough and sputum production. Therefore, in our study, these symptoms were evaluated based on their occurrence over the preceding week. As these parameters reflect the subjective assessments of the enrolled patients, it is not possible to define a minimal clinically important difference (MCID).

3. Outcomes

The primary objective of the RESPONSE study was to evaluate the change in patients' symptom scores, as measured by the *COPD Assessment Test* (CAT), after six months of treatment with extrafine BDP/FF/G via dry powder inhaler (DPI).

Secondary endpoints included proportion of patients achieving CAT improvement higher than the MCID; changes in FEV_1 and FVC Forced Vital Capacity (FVC) values over the six-month treatment period compared to baseline; changes in quality of life assessed by the EQ-5D-3L questionnaire and the Visual Analogue Scale (VAS); changes in the self-reported frequency of coughing and sputum production; changes in oxygen saturation (SpO_2); assessment of adherence to inhalation therapy using the Test of Adherence to Inhalers (TAI-12) questionnaire; and evaluation of changes in the severity of dyspnea using the modified Medical Research Council (mMRC) scale.

Furthermore, an explorative analysis of diseases stability was performed. Patients were considered responders to treatment if there was no significant and clinically relevant deterioration in lung function (FEV_1 decrease of 100 mL or more), CAT scores (2 points or more) and no exacerbations happened during the study period. This definition was developed, based on the work of *Singh* et al. [3].

Finally, a multivariate regression analysis was performed to determine patient characteristics contributing to higher improvement in each outcome measures.

4. Statistical analysis

Baseline characteristics were summarized by initial therapy group and for the total cohort. Distributions were calculated for categorical variables, while continuous variables were presented as means with standard deviations. Changes in the CAT scores were calculated within each treatment group based on preceding therapy and in the pooled dataset. Paired-sample t-tests were used to assess whether within-group changes from baseline in CAT scores and other continuous secondary outcomes were statistically significant. For categorical endpoints, exact binomial tests were applied to evaluate whether the proportions of patients showing improvement versus worsening differed significantly from a 50:50 distribution.

In the multivariate analysis, for numerical variables, we used ANOVA. We included all the subgroup variables in the first model with their paired interactions: Gender; Age groups: 38–62, 63–70 and 70–90 cohorts; the same thresholds as in the Bulgarian study; FEV_1: severe (<50 %) and moderate airflow limitation; Treatment before enrolment: ICS-LABA, LABA-LAMA, other; Smoking status: Active smoker, ex-smoker and non-smoker; Severe exacerbation: at least one or none. We used AIC-based model selection to get an intermediate model. Many of them contained non-significant interactions. We simplified those models further - based on AIC again - and removed non-significant interactions or variables, while the smaller model was not significantly different from the original model. The age group, sex and exacerbation were included in each model.

5. Results

The enrolment period for the study spanned from March 27, 2023, to April 30, 2024. The last patient last visit (LPLV) was recorded on October 31, 2024. A total of 1585 individuals were enrolled, and 1336 participants completed the study. Accordingly, 249 patients (15.7 %) were excluded from the final analysis, primarily due to loss to follow-up. Patient flow is shown on Fig. 1.

Among the studied cohort, 672 participants (50.3 %) were women. Of the enrolled, 727 patients (54.42 %) were current smokers, 470 (35.18 %) were former smokers, and 139 (10.40 %) had never smoked. The mean BMI was 27.9, indicating that the population was, on average, classified as overweight.

In the 12 months preceding enrolment, 86 % of patients reported no severe exacerbations, 14 % experienced at least one episode. During the

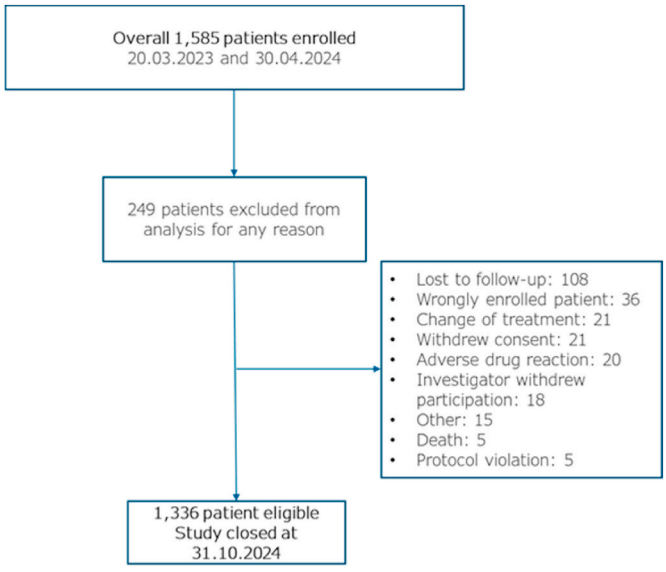

Fig. 1. Patient flow of the RESPONSE study.

same period, 82.4 % of patients experienced two moderate exacerbations. The mMRC scale indicated that the majority of patients were symptomatic, predominantly scoring between 2 and 3. The average CAT score at baseline was 20.49, reflecting a moderate level of symptom burden. The mean SpO_2 was 95.26 %. The mean post-bronchodilator FEV_1 % was 52.27 %. EQ-5D questionnaire revealed that most patients experienced some level of limitation across all five dimensions, average baseline VAS score was 59.11. The key baseline characteristics of the enrolled patients are summarized in Table 1.

5.1. Symptoms and symptom scores

According to the CAT questionnaire, an average reduction of 6.32 points (Fig. 2) was recorded after six months of therapy (95 % CI: 6.00–6.65; $p < 0.001$), which substantially exceeded the MCID of 2-point improvement [19].

Overall, 81.0 % of all patients achieved a CAT score improvement higher than the MCID values.

An analysis of individual CAT items revealed the following mean improvements after six months of treatment: 1.02 points for cough, 1.04 for sputum production, 0.72 for chest tightness, 0.88 for breathlessness, 0.78 for activity-related quality of life limitations, 0.59 for confidence when leaving home, 0.67 for sleep quality, and 0.61 for overall energy level (Table 2, **A**).

The reductions in CAT scores observed among patients previously treated with LABA/LAMA or ICS/LABA combinations were also statistically significant across all individual CAT items when compared to baseline. (Table 2, **B**). Distributions of patients according to the level of improvement in each domain and overall are shown in Supplementary material 2.

According to the participants' subjective self-report, 29.57 % of patients reported that their cough resolved completely, while in 67.89 % symptoms remained unchanged and in 2.54 % coughing emerged during the study period. Similarly, sputum production resolved in 38.55 % of patients, in 57.56 % remained unchanged, and in 3.89 % sputum production emerged as a new symptom.

Significant improvement was also observed in dyspnea, with 36.47 % of patients showing better mMRC scores (58.76 % no change, 4.75 % worsening) after six months of treatment.

Table 1
Baseline Characteristics of Enrolled Patients. Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; FEV1, Forced Expiratory Volume in 1 s; HRQoL, Health Related Quality of Life; VAS, Visual Analogue Scale. TAI-12: Test of Adherence to Inhalers (12-item questionnaire).

		All Patients (N = 1336)	Switched from LABA/LAMA (N = 792)	Switched from ICS/LABA (N = 544)
Sex	**Male**	49.7 %	50.3 %	48.9 %
	Female	50.3 %	49.8 %	51.1 %
Age		67 ± 8.6	66.9 ± 8.6	67.1 ± 8.6
Body Mass Index		28 ± 6.5	27.7 ± 6.4	28.3 ± 6.6
Smoking habits	**Smoker**	34 %	57.5 %	50 %
	Ex-smoker	35 %	35.4 %	34.9 %
	Nonsmoker	10 %	7.2 %	15.1 %
Highest level of education	**Primary school**	45 %	44.9 %	45 %
	Secondary school	50.2 %	49.5 %	51.3 %
	University	4.8 %	5.6 %	3.7 %
Occupation	**Blue collar**	26.9 %	25.4 %	29.2 %
	White collar	7.2 %	6.9 %	7.5 %
	Retired	58.9 %	60.7 %	56.3 %
	Retired with disability	7 %	6.9 %	7 %
COPD Assessment Test score		20,5 ± 7	19.6 ± 6.5	21.7 ± 7.5
Number of moderate exacerbations	**0**	3.9 %	3.9 %	3.9 %
	1	5.1 %	5.4 %	4.6 %
	2	82.4 %	84 %	80.2 %
	≥3	8.6 %	6.7 %	11.4 %
Number of severe exacerbations	**0**	86 %	85.6 %	86.6 %
	1	12.7 %	13.5 %	11.4 %
	2	1.2 %	0.8 %	1.8 %
	≥3	0.2 %	0.1 %	0.2 %
Average FEV_1 %		52.3 ± 13	52.8 ± 13	51.5 ± 12.9
Average FEV_1 (l)		1.3 ± 0.5	1.4 ± 0.5	1.3 ± 0.5
Coughing as a symptom present		90 %	90.2 %	89.9 %
Sputum as a symptom present		81.1 %	82.1 %	79.8 %
HRQoL VAS score (0–100)		59,1 ± 15.2	59 ± 14.9	59.2 ± 15.6
TAI-12 Adherence (applying items 1 to 10)	**TAI<46** Poor adherence	35.9 %	30.7 %	43.6 %
	TAI ≤ 46 < 50 Moderate adherence	15.8 %	17.1 %	14.2 %
	TAI = 50 Good adherence	48.2 %	52.3 %	42.3 %

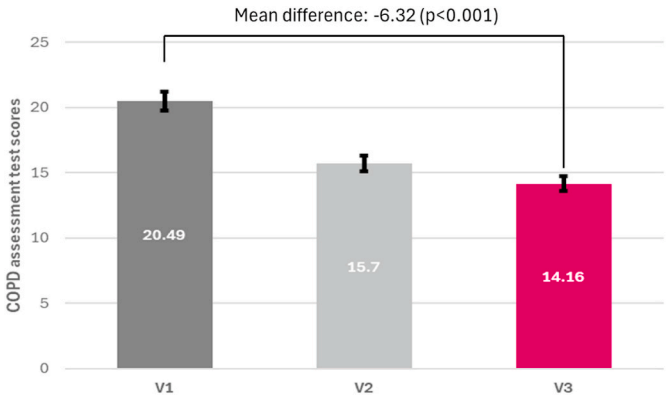

Fig. 2. Changes in CAT scores from baseline to V3 in all patients.

5.2. Quality of life

On the VAS scale, which reflects patients' perceived health status, a mean improvement of 12.14 points was observed after six months (95 % CI: 11.3–12.98, $p < 0.001$) which far exceeded the MCID of 8 points [20] for VAS.

There was a significant improvement in all domains of EQ-5D-3L, with the proportion of patients not reporting any limitations in all domains increasing over the study period. Detailed proportions are shown in Fig. 3.

5.3. Adherence

TAI-12 (*Test of Adherence to Inhalers*) scores (including all 12 questions) showed an average improvement of 3.66 points (95 % CI: 3.23–4.09, $p < 0.001$). Analysis of the TAI-12 questionnaire data (applying items 1 to 10) revealed that adherence improved in 435 patients (32.56 %) compared to their baseline adherence category, declined in 46 patients (3.44 %), and remained unchanged in 855 patients (64.00 %).

When adherence categories were determined using the first ten questions based on patients' self-reported responses, analysis showed a significant decrease in the percentage of patients with poor adherence and a significant increase in those with good adherence by Visit 3 (Table 3).

In terms of the whole TAI-12 (including all 12 questions), there was a significant improvement in all domains: TAI 1–5 (sporadic adherence), 6–10 (deliberate adherence, and 11–12 (unconscious adherence) (Fig. 4).

Table 2
Mean CAT scores and changes in each CAT subquestion compared to baseline, after 6 months of treatment assessing (**A**): all patients attending Visit 3 and (**B**): patients previously treated with LABA/LAMA or ICS/LABA combinations. Scale: 0 (best possible health status) to 5 (worst possible health status). All eight modules demonstrated significant reductions across LABA-LAMA, ICS-LABA, and the overall patient cohort ($p < 0.0001$ for all comparisons).

A	All Patients who attended Visit 3 (N = 1336)			B	Switched from LABA/LAMA (N = 792) or ICS/LABA (N = 544)		
	Average CAT scores at V1	Average CAT scores at V3 [*change*]	P-values assessing improvement from V1 to V3.		Average CAT scores at V1	Average CAT scores at V3 [*change*]	P-values assessing improvement from V1 to V3.
Cough	2.96 ± 1.1	1.94 ± 0.92 [*-1.02 ± 1.14*]	$p < 0.0001$	LABA/LAMA	2.91 ± 1.11	1.93 ± 0.95 [-0.98 ± 1.14]	$p < 0.0001$
				ICS/LABA	3.03 ± 1.08	1.95 ± 0.87 [-1.08 ± 1.14]	
Phlegm	2.67 ± 1.19	1.63 ± 1 [*-1.04 ± 1.23*]		LABA/LAMA	2.63 ± 1.21	1.62 ± 1.04 [-1 ±1.24]	
				ICS/LABA	2.74 ± 1.17	1.64 ± 0.95 [-1.1 ± 1.23]	
Tightness in the chest	1.93 ± 1.41	1.21 ± 1.03 [*-0.72 ± 1.21*]		LABA/LAMA	1.74 ± 1.37	1.07 ± 0.99 [-0.67 ± 1.19]	
				ICS/LABA	2.21 ± 1.42	1.42 ± 1.06 [-0.79 ± 1.23]	
I walk up a hill	3.55 ± 1.02	2.67 ± 1.03 [*-0.88 ± 1.14*]		LABA/LAMA	3.52 ± 1	2.64 ± 1.05 [-0.88 ± 1.18]	
				ICS/LABA	3.6 ± 1.04	2.71 ± 1 [-0.89 ± 1.07]	
Home activity	2.48 ± 1.39	1.70 ± 1.17 [*-0.78 ± 1.23*]		LABA/LAMA	2.35 ± 1.37	1.61 ± 1.19 [-0.75 ± 1.29]	
				ICS/LABA	2.66 ± 1.38	1.83 ± 1.14 [-0.83 ± 1.13]	
I leave my home	1.70 ± 1.5	1.11 ± 1.09 [*-0.59 ± 1.13*]		LABA/LAMA	1.45 ± 1.42	0.93 ± 1.02 [-0.53 ± 1.1]	
				ICS/LABA	2.06 ± 1.53	1.38 ± 1.15 [-0.69 ± 1.17]	
I sleep soundly	2.18 ± 1.42	1.51 ± 1.09 [*-0.67 ± 1.23*]		LABA/LAMA	2.04 ± 1.41	1.36 ± 1.07 [-0.68 ± 1.24]	
				ICS/LABA	2.38 ± 1.4	1.73 ± 1.1 [-0.65 ± 1.22]	
Energy	3.01 ± 1.01	2,40 ± 0.88 [*-0.61 ± 1.07*]		LABA/LAMA	2.98 ± 0.99	2.38 ± 0.88 [-0.6 ± 1.08]	
				ICS/LABA	3.05 ± 1.03	2.42 ± 0.88 [-0.63 ± 1.06]	

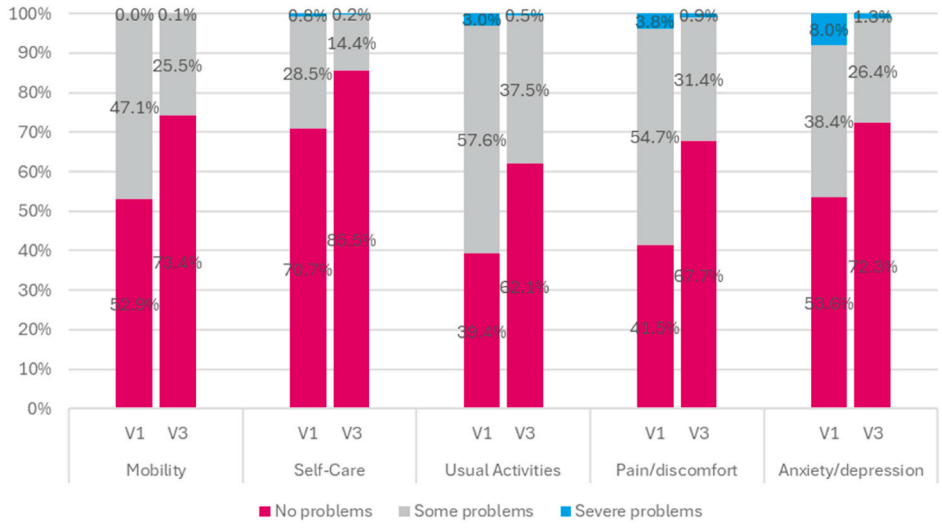

Fig. 3. Change in E5-5D-3L domains between baseline (V1) and Visit 3 (V3).

5.4. Pulmonary function and oxygen saturation

Both FEV_1 and FVC improved over the treatment period. FEV_1 increased by 0.12 L (95 % CI: 0.1–0.14, $p < 0.001$) (Fig. 5) exceeding the MCID of 100 mL and FVC improved by 0.07 L (95 % CI: 0.04–0.11, $p < 0.001$). The MCID FVC in COPD is not as well-established as it is for FEV_1. Notably, FVC is more influenced by patient effort and exhibits greater variability than FEV_1[21–23]

After six months of treatment with BDP/FF/G 88/5/9 μg DPI, 18.56 % of patients demonstrated an improvement in oxygen saturation, reaching normal levels ($SpO_2 \geq 95$ %) compared to baseline, while 75.45 % showed no change and 5.99 % experienced a decline ($SpO_2 < 95$ %) in saturation.

Table 3
Percentage of patients showing different levels of adherence (as per TAI) at Visits 1 and 3. Scale: TAI<46: poor adherence; TAI≤46 < 50: moderate adherence; TAI = 50: good adherence.

	V1 (percentage of patients)	V3 (percentage of patients)	P-values assessing changes from V1 to V3
TAI<46 [Poor adherence]	35.93 %	16.47 %	$p < 0.0001$
TAI ≤ 46 < 50 [Moderate adherence]	15.87 %	11.75 %	
TAI = 50 [Good adherence]	48.20 %	71.78 %	

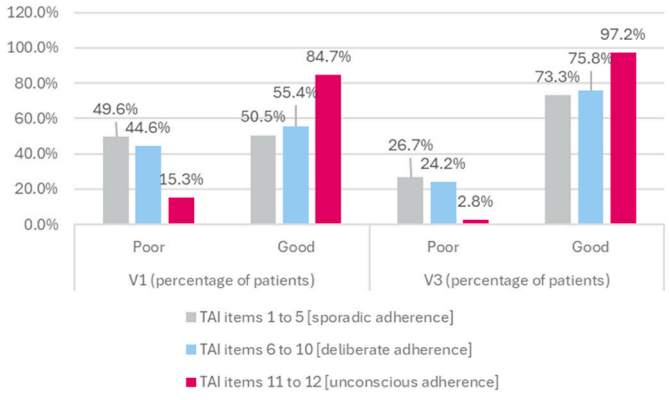

Fig. 4. Assessment of types of non-adherence. $p < 0.0001$ in all cases.

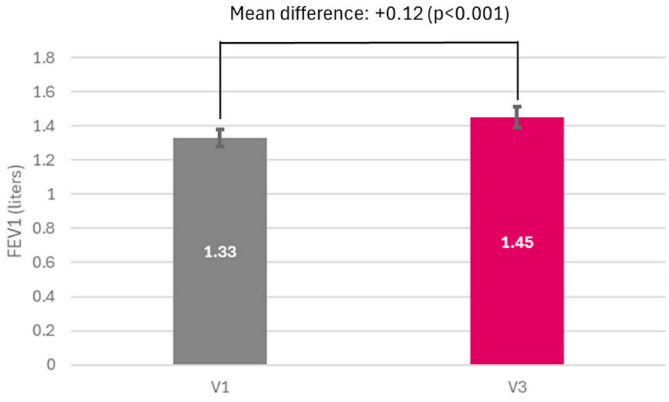

Fig. 5. After six months of treatment with BDP/FF/G 88/5/9 µg DPI, FEV1 (l) improved significantly with 120 mL.

5.5. Exacerbations

Proportion of patients reporting any number of severe exacerbations during the 6 months of the study was 3.7 % (1 event), 0.5 % (2 events) and 0.2 % (3 or more events). 95.7 % of the patients did not suffer a severe exacerbation. At the same time proportions reporting moderate exacerbations were 13.9 % (1 event), 17.6 % (2 events) and 2.3 % (3 or more events), with 66.2 % not reporting any exacerbations.

With only 6 months follow-up, comparison of exacerbations rates to baseline was not appropriate so no direct comparison was made.

5.6. Disease stability

Over the six-month observation period, 53 % of patients met our criteria for disease stability (Fig. 6). Exacerbations occurred in 28 %, FEV_1 decline in 11 %, CAT worsening in 1 %, and 7 % showed deterioration in two or more of the assessed domains.

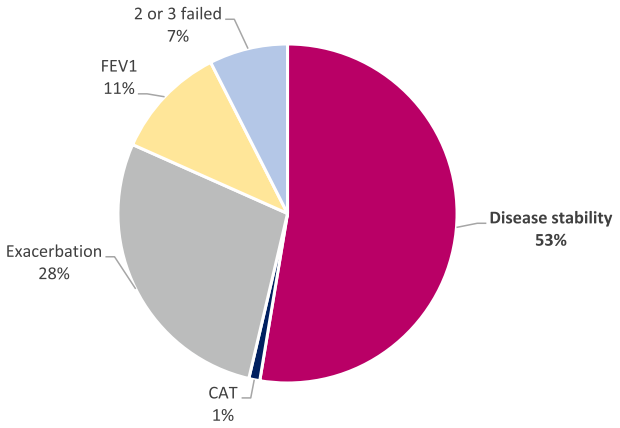

Fig. 6. Response rate after six months of treatment with BDP/FF/G 88/5/9 µg DPI, with labels indicating the reasons patients did not achieve disease stability.

5.7. Multivariate analyses

For each endpoint, there were multiple factors significantly effecting treatment outcomes, however there were no clear baseline parameters affecting all or multiple outcome measures. Along with this issue, most outcomes were affected by multiple parameters and their interactions, resulting in a clinical impossible interpretation of these results. Due to the large size of these computations, the detailed results are shown in Supplemental material 1.

5.8. Safety

During the study, adverse drug reactions (ADR) related to BDP/FF/G 88/5/9 µg DPI were reported to the sponsor in a total of 24 patients, of which 20 cases resulted in discontinuation of treatment. In six cases, the reporters assessed the events as "not related to the treatment", but this was later upgraded to „related to BDP/FF/G 88/5/9 µg DPI" by the Marketing Authorization Holder (Chiesi Farmaceutici S. p.A., the parent company of the sponsor) in the final assessment. Finally, the adverse events were associated with the use of BDP/FF/G 88/5/9 µg DPI at certain level in 7 (29 %), at probable level in 9 (38 %) and at possible level in 8 (33 %) cases. In 22 of the 24 cases, non-serious adverse drug reactions, mainly skin symptoms, fungal infection of the oral cavity and pharynx, gastrointestinal complaints were reported, while in two cases the reported adverse drug reactions were serious (COPD exacerbation, atrial fibrillation, pneumonia), both resulting in hospitalization.

The ADRs reported during the study did not impact the known benefit-risk profile of BDP/FF/G 88/5/9 µg DPI and did not make any change of the SmPC or the implementation of additional risk minimisation measures necessary.

6. Discussion

The RESPONSE study is the first real-world study evaluating BDP/FF/G 88/5/9 µg DPI in patients with various clinical COPD phenotypes who were previously treated with dual inhalation therapy. In our study, we assessed the therapeutic efficacy in line with the major treatment goals of COPD as detailed by the GOLD guidelines: reduction of symptoms, improvement of quality of life, mitigation of risk factors, and prevention of exacerbations. Following the switch to BDP/FF/G 88/5/9 µg DPI, we observed clinically relevant and statistically significant improvements across all evaluated endpoints after six months. Our results demonstrated that the triple inhalation therapy with BDP/FF/G 88/5/9 µg DPI positively influenced symptoms, lung function, adherence, and

quality of life.

According to the CAT questionnaire, which summarizes patients' symptoms, substantial improvement was noted far exceeding the MCID of 2 points [19]. The highest improvement was seen in the questions of cough, sputum production, and dyspnea. This finding was consistent with the significant improvements in self-reported frequency of cough and sputum production. Even though these symptoms are usually considered inherent to COPD, it is important to keep in mind that with the appropriate treatment and device selection their burden can be substantially mitigated.

Further analysis of CAT questions showed a very different level of limitation in each domain, reflecting the high variability of COPD symptoms. Even though cough and sputum production along with dyspnoea are considered the most common symptoms of COPD, baseline scores were highest at the questions assessing energy and physical exertion capacity. This highlights the importance of a thorough assessment of patients' symptoms to uncover symptom severity. It also worth mentioning that the highest improvements were not seen at the most affected dimension of symptoms. Further studies are needed to find the most appropriate treatment approach for each symptom category.

Analysis of CAT score trajectories from V1 to V3 demonstrated clinically relevant improvements in patients previously receiving either LABA/LAMA or ICS/LABA maintenance therapy. In the LABA/LAMA cohort, consistent reductions in CAT scores were observed across all questions, with mean changes ranging from −0.53 to −1.00. In the ICS/LABA cohort, the improvements were slightly greater, with reductions ranging from −0.63 to −1.10. On average, patients in the ICS/LABA group exhibited slightly greater improvements in CAT scores compared to those in the LABA/LAMA group (mean change of −0.83 vs −0.76, respectively). However, no notable differences were observed between specific CAT domains across the two previous treatment groups.

In comparison with the similarly designed real-world RATIONALE [14] study, which utilized the BDP/FF/G 87/5/9 μg pMDI (pressurized metered-dose inhaler) formulation, our results strongly support international findings. Both studies showed significant improvement in CAT, quality of life, adherence and oxygen saturation with the favourable impact of triple therapy over previous dual therapy clearly demonstrated. However, an important difference lies in the device used: while the RATIONALE study employed the pMDI, RESPONSE provides valuable new real-world data on the use of the NEXThaler device, for which fewer previous data were available.

Adherence to inhalation therapy remains a persistent challenge in COPD management. In our study, the TAI-12 questionnaire revealed a 3.66-point increase (applying to items 1 to 12) in adherence scores after switching to BDP/FF/G 88/5/9 μg DPI. This may reflect the benefits of twice-daily, single-inhaler triple therapy in improving treatment adherence through simplification and ease of use. An analysis of non-adherence patterns revealed significant improvements across all three categories—occasional, deliberate, and unintentional—by Visit 3 (V3). A common critique of addressing adherence in studies is the assumption that just the enrolment in the study increases patient's adherence as more focus is directed to their management. However, in a non-interventional setting, the effect of the study on the patient is minimal and mostly could only stem from a low increase of the physicians' attention to the patients. It is important to highlight that even a minimal change in management can have a very substantial effect on adherence. This approach of more focused assessment of adherence could be incorporated to everyday clinical practice.

Disease stability, as an increasingly emphasized therapeutic objective, was also evaluated. Over the six-month follow-up period, more than half of the patients met the stability criteria (no clinically significant deteriorations were observed, meaning no exacerbation, no FEV_1 decline, and no CAT score increase), supporting the beneficial role of BDP/FF/G 88/5/9 μg DPI in maintaining disease control and showing that disease stability can be a realistic goal of COPD treatment. It is important to highlight, that most of our patients who failed to reach stability, did so due to exacerbations. This finding further highlights the importance of a holistic approach to treatment, involving non-pharmaceutical interventions beyond appropriate medication treatment.

The relevance of identifying a clinically relevant deterioration [24] lies in its prognostic implications: patients experiencing deterioration in at least one of these domains demonstrate significantly worse long-term outcomes, including an elevated risk of exacerbations and mortality over a 12- to 36-month period [25–27]. As emphasized by *Singh* et al., disease stability can be achieved in one or more of these domains, depending in part on the availability of diagnostic tools such as spirometry. The identification of unstable domains presents an opportunity to tailor individualized management strategies aimed at improving overall disease control [3].

Our multivariate analyses did not reveal a consistent clinically significant and reliable subgroup associations that might predict higher response rate for BDP/FF/G DPI treatment. However, these findings may reflect individual therapeutic responses observed in clinical practice and underscore the importance of personalized treatment approaches in COPD management.

Peripheral blood eosinophil count (BEC) represents a key consideration in COPD management. The RESPONSE study was initiated in 2022, coinciding with the GOLD 2022 report, which identified BEC as a practical biomarker to guide inhaled corticosteroid (ICS) therapy for exacerbation prevention. GOLD emphasized a continuous relationship between eosinophil levels and ICS response, with greater benefit at higher counts, and suggested approximate thresholds: $<$100 cells/μL (low likelihood of benefit), 100–300 cells/μL (intermediate), and $\geq$300 cells/μL (high). Importantly, BEC should be interpreted alongside exacerbation history and clinical context, as counts may fluctuate over time. While GOLD 2022 supports individualized ICS decisions based on BEC, the Hungarian national COPD guideline at that time had not yet incorporated these recommendations. Consequently, the RESPONSE study—conducted in a non-interventional setting—was unable to evaluate associations between BEC and exacerbation reduction. The most recent Hungarian guideline update, issued in March 2024, aligned with GOLD's BEC-related recommendations, making them available to Hungarian pulmonologists. Nonetheless, routine BEC measurement in outpatient pulmonology practice remains non-reimbursed in Hungary.

The latest GOLD Science Committee Report [28] emphasizes distinguishing volume and flow responders in COPD diagnosis. Volume responders show greater FVC than FEV_1 improvement post-bronchodilator, revealing obstruction otherwise missed, often due to gas trapping or airway collapse. Flow responders improve more in FEV_1, potentially reclassifying from obstructive to non-obstructive, yet remain at elevated risk and require monitoring. These patterns reinforce the necessity of post-bronchodilator spirometry to accurately identify at-risk patients. In the RESPONSE study, lung function was assessed using FEV_1, FVC, and FEV_1/FVC only, as body plethysmography —similar to BEC monitoring —is not routinely performed in outpatient pulmonology practice in Hungary, as plethysmography equipment is generally unavailable in these centers. Therefore, the assessment of changes in lung volumes and specific airway resistance (sRAw) was not feasible within the scope of the RESPONSE study.

This study has several limitations. As a real-world, non-randomized observational study, it lacks a control group, which restricts the ability to attribute changes exclusively to the intervention. Additionally, patient-reported outcomes such as CAT, mMRC, and VAS are subjective and may be influenced by individual perceptions or external factors. Another limitation of this study is that the six-month observation period may be insufficient to reliably evaluate the therapeutic effects on COPD exacerbations. Considering that the rates of exacerbations are different according to seasons, data collection from less than 12 months makes annualized rates unreliable. Nonetheless, given that these data were collected, we deemed it appropriate to include and report them. Accordingly, while the six-month follow-up period is adequate for

assessing short-term outcomes, it does not permit conclusions regarding long-term efficacy. Strengths of our study stem from its large sample size, the consistent management of patients by respiratory specialists, and its conduct within real-life clinical settings, enabling all COPD patients to be enrolled.

7. Conclusion

The RESPONSE study is the first real-world analysis to evaluate the effectiveness of BDP/FF/G 88/5/9 μg DPI in a broad COPD population previously treated with dual inhaled therapy. The results demonstrate significant clinical improvements in symptoms, lung function, quality of life, adherence, and overall disease stability over a six-month period. These findings support the use of single-inhaler triple therapy as a viable and effective option for patients with symptomatic COPD who remain uncontrolled on dual therapy.

CRediT authorship contribution statement

Viktória Dulai: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Conceptualization. **András Keglevich:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Balázs Sánta:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Zsolt Abonyi-Tóth:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Ildikó Horváth:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Disclosure

B. Santa, and A. Keglevich are employees of Chiesi Hungary Kft. I. Horváth has received lecture or consultancy fees and/or support for conference attendance from AstraZeneca, Berlin-Chemie-Menarini, Boehringer-Ingelheim, Chiesi, Orion Pharma, and Sanofi. The authors report no other conflicts of interest in this work.

Ethics approval and informed consent

The study was approved by the National Institute of Pharmacy and Nutrition (approval No.: OGYÉI/78232-4/2022) based on the beneficial assessment of the National Scientific and Research Ethics Committee of Hungary and was conducted according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Viktoria Dulai reports financial support was provided by Chiesi Hungary Kft. Andras Keglevich, Balazs Santa reports a relationship with Chiesi Hungary Kft that includes: employment. Zsolt Abonyi-Toth reports a relationship with Chiesi Hungary Kft that includes: consulting or advisory. Ildiko Horvath reports financial support provided by Chiesi Hungary. She also reports a relationship with AstraZeneca, Berlin-Chemie -Menarini Kft, Chiesi Hungary and Sanofi that includes: consulting or advisory and speaking and lecture fees.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2025.108498.

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