Original Research

Validation of the Onset of Effect Questionnaire in Participants With Chronic Obstructive Pulmonary Disease

Charlie Strange, MD[1] Barry J. Make, MD[2] Frank J. Trudo, MD, MBA[3] Gale Harding, MA[4] Danielle Rodriguez, PhD[5] James M. Eudicone, MS, MBA[3] Norbert Feigler, MD[3] Hitesh N. Gandhi, MBBA, MHA, MAS[6]

[1]Division of Pulmonary and Critical Care Medicine, Medical University of South Carolina, Charleston, South Carolina, United States

[2]Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colorado, United States

[3]BioPharmaceuticals Medical, AstraZeneca, Wilmington, Deleware, United States

[4]Evidera, Bethesda, Maryland, United States

[5]Evidera, Seattle, Washington, United States

[6]Alexion, AstraZeneca Rare Disease, Wilmington, Delaware, United States

Address correspondence to:
Charlie Strange, MD
Division of Pulmonary and Critical Care Medicine
Medical University of South Carolina
Charleston, SC, USA
Phone: (843) 792-3174
Email: strangec@musc.edu

Running Head: **Validation of the OEQ in Participants With COPD**

Keywords: chronic obstructive pulmonary disease; patient-reported outcome; Onset of Effect Questionnaire

Abbreviations: COPD, chronic obstructive pulmonary disease; OEQ, Onset of Effect Questionnaire; SABA, short-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta-agonist; ICS, inhaled corticosteroid; CE, concept elicitation; CI, cognitive interviewing; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PGIS, Patient Global Impression of Severity; PEF, peak expiratory flow; NiSCI, Nighttime Symptoms of COPD Instrument; EXACT-PRO, Exacerbations of Chronic Obstructive Pulmonary Disease Tool – Patient-Reported Outcomes PGIC, Patient Global Impression of Change; C-PPAC, PROactive Physical Activity in COPD; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICC, Intraclass correlation; SD, standard deviation; IQR, interquartile range; P, period; mL, milliliter; IC, inspiratory capacity; s, second

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Financial Support:
This study and medical writing support were funded by AstraZeneca.

Date of Acceptance: May 1, 2024 | ***Publication Online Date***: May 7, 2024

Citation: Strange C, Make BJ, Trudo FJ, et al. Validation of the Onset of Effect Questionnaire in participants with chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis.* 2024; Published online May 7, 2024.
https://doi.org/10.15326/jcopdf.2023.0485

This article has an online supplement.

Abstract

Background: Patient perception of medication onset of effect is important for adherence. Although the Onset of Effect Questionnaire (OEQ) has been validated in patients with asthma, it has not been evaluated in patients with chronic obstructive pulmonary disease (COPD). This study evaluated the COPD-OEQ in patients with COPD.

Methods: Two analyses (qualitative and quantitative) were conducted to assess the content validity and psychometric properties of the COPD-OEQ in participants with COPD. In the qualitative analysis, interviews assessed content validity by concept elicitation (CE) and cognitive interviewing (CI). CE included questions to understand patient experience related to onset of medication effect. CI included completion of the COPD-OEQ and assessment of the COPD-OEQ items, response options, and instructions. During the 2-week quantitative analysis, 2 versions of the COPD-OEQ (Weekly and Daily) were administered to assess test-retest reliability, construct validity, and known-groups validity.

Results: The qualitative analysis demonstrated that 3 of the 5 COPD-OEQ items were relevant and understood as intended. Qualitative findings demonstrated inconsistent evidence that the COPD-OEQ Weekly and Daily were reliable and valid measures in participants with COPD. Test-retest reliability was observed for the COPD-OEQ Weekly and Daily; however, construct validity was weak and demonstrated inconsistent correlations among COPD-OEQ items. Overall, known-groups validity was not demonstrated.

Conclusion: The weak evidence from the quantitative analysis of the COPD-OEQ Weekly and Daily tools does not support use of the OEQ in general COPD. The study supports the content validity for the assessment of perceived onset of effect in patients with COPD.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Introduction

Chronic obstructive pulmonary disease (COPD) remains a leading cause of death worldwide[1] and is associated with a high economic and social burden.[2] A major goal of therapy in COPD is to improve lung function and provide symptom relief. Effective management of COPD has been shown to reduce exacerbations, reduce hospitalizations, improve health-related quality of life, and reduce mortality.[3] Adherence to prescribed inhaled medications is key in the management of patients with COPD in both clinical and ambulatory settings.[4] The consequences associated with non-adherence include increased risk of poor clinical outcomes, worsening quality of life, higher mortality rate, increased number of relapses, and increased health care expenses.[5,6] Adherence is further complicated because patients with COPD are often diagnosed with other diseases that greatly affect self-management of medications and financial burden.[5,6] It has been suggested that patient adherence is lower for medications that do not have an immediate or direct effect on symptoms.[7] Evidence demonstrates that nonadherent patients may be more likely to adhere to therapy if they could feel an immediate symptomatic benefit.[8,9] The onset of action of a prescribed therapy may help patients adhere to their daily regimen because the patient perceives an immediate improvement from their medication.[9,10] To date, research regarding the onset of effect of prescribed inhaled medications in COPD populations is limited.

The Onset of Effect Questionnaire (OEQ) consists of a 5-item patient-reported outcomes questionnaire that was originally developed for patients with asthma to evaluate patient perceptions related to the onset of action of maintenance medication.[8,11] The OEQ items were as follows:

1. During the past week, you could tell your study medication was working.
2. During the past week, you could feel your study medication begin to work right away.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

3. During the past week, you felt physical sensations shortly after taking your study medication that reassured you that it was working.
4. During the past week, your study medication worked as quickly as albuterol.
5. During the past week, you were satisfied with how quickly you felt your study medication begin to work.

Each OEQ item was evaluated using a 5-point scale, including: "strongly disagree," "somewhat disagree," "neither agree nor disagree," "somewhat agree," and "strongly agree."[8] Two of the OEQ items (Items 2 and 5) have demonstrated reliability and content validity in patients with asthma and support use in future clinical trials to evaluate asthma maintenance treatment.[11] Although content validity is reported in patients with asthma, the OEQ has not been evaluated in patients with COPD. The purpose of this study was to evaluate the qualitative and psychometric properties of the OEQ in patients with COPD.

Methods

Phase 1: Content Validity Qualitative Analysis

Specific Aims

The primary objective of the qualitative analysis was to evaluate the content validity of the 5 items of the OEQ in participants with mild to very severe COPD based on qualitative interviews.

Participants

Qualitative analysis participants were recruited from 4 US-based clinical sites that identified the participants, verified eligibility, assisted with scheduling interviews, and completed a clinical information form for each participating patient. Participants included in this analysis were ≥40 years of age, had a spirometrically confirmed diagnosis of COPD, and were treated with any of

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

the following therapies for COPD for ≥3 months prior to screening: long-acting muscarinic antagonist (LAMA), long-acting beta-agonist (LABA) + LAMA, inhaled corticosteroid (ICS) + LABA, ICS + LABA + LAMA, or SABA only. Any potential participants were excluded if they participated in a clinical trial with study interventions within 45 days of screening or had a diagnosis of any chronic respiratory conditions other than COPD. The analysis protocols were approved by a central institutional review board (Ethical & Independent Review Services), and all participants provided written informed consent prior to data collection procedures.

Interview methods

One-on-one qualitative interviews were conducted in person or by telephone by trained interviewers using a semi-structured interview guide and a combined approach of concept elicitation (CE) and cognitive interviewing (CI). The CE portion of the interview included open-ended questions to understand the patient's experience of being able to feel the onset of their medication's effects and, additionally, captured the patient-reported length of time to feel the medication working. The CI portion included completion of the COPD-OEQ, followed by an interview to assess the relevance and understandability of the COPD-OEQ items, response options, and instructions. Participants also completed a sociodemographic form, and sites completed a clinical questionnaire for purposes of sample description.

Analyses

The COPD Assessment Test™ (CAT) and medication class were used to describe the sample population. For qualitative data analyses, a content analysis approach was used to investigate the interview data (based on notes, interview transcripts, and audio recordings). These data were analyzed using a qualitative analysis software program, ATLAS.ti, which allows for systematic assessment of the concepts and themes expressed by participants during the interview

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

discussions. A coding scheme was developed based on analysis objectives and the interview guide. For the CE portion, thematic codes were designed to capture general themes associated with the patient's experience of being able to feel the onset of their medication effects. The CI portion featured codes designed to focus on the clarity, content, relevance, and interpretation consistency of the COPD-OEQ.

Phase 2: Psychometric Properties Quantitative Analysis

The secondary phase of this study included a 2-week observational assessment to examine the psychometric properties of the COPD-OEQ, including reproducibility, construct validity, and predictive validity of each COPD-OEQ item.

Specific Aims

The primary objective of the quantitative analysis was to examine the psychometric properties of the COPD-OEQ items, including validity (convergent and known groups) and reliability (test-retest) using a daily recall (COPD-OEQ Daily) and 7-day recall (COPD-OEQ Weekly) period. The reproducibility of COPD-OEQ Items 1 (working), 2 (working right away), and 5 (satisfied) was assessed among a group of heterogeneous but stable patients. Convergent validity was used to assess the extent to which the measure being evaluated related to other variables or to which it is expected to be related. Known-groups validity was examined by grouping participants into varying levels of disease severity and disease status, and test-retest reliability assessed the consistency of the outcomes by repeating the same assessment. The secondary objective of this analysis was to determine whether participants respond similarly to the COPD-OEQ Weekly versus Daily. Additional exploratory outcomes sought to evaluate responses to the COPD-OEQ items by medication class and to determine correlations between COPD-OEQ Weekly and Daily items.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Participants

Quantitative analysis participants were recruited from 12 clinical sites in the United States, where site investigators verified initial eligibility. Participants included in this analysis were ≥40 years of age, had a confirmed diagnosis of COPD, had a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <0.70 and FEV_1 percentage (%) predicted between 30% and 79% post-bronchodilator medication and were treated with any of the following COPD controller medications for ≥3 months: LAMA, LABA + LAMA, ICS + LABA, or ICS + LABA + LAMA. Five participants who enrolled prior to the COVID-19 pandemic were excluded from the final analysis population because of procedural additions to the protocol after the start of the pandemic.

Study design

This analysis included 3 clinical site visits (screening, baseline visit, and final visit). Participants were instructed to withhold their controller medication for 12 to 24 hours (depending on the prescribed interval) and to not use their rescue medication for 6 hours prior to the baseline visit. At the baseline visit, a weekly version of the COPD-OEQ was evaluated with a 7-day lookback before medications were taken or spirometry was performed. Then, spirometry was conducted before and 1 to 2 hours after participants took their maintenance inhalers, with differences recorded. Thereafter, the COPD-OEQ Daily was repeated 1 hour after maintenance inhaler use in the morning. During the baseline visit, participants also completed several questionnaires, including the CAT and the Patient Global Impression of Severity (PGIS). Prior to leaving the baseline visit, participants were provided with a peak flow meter to capture morning and evening peak expiratory flow (PEF) and were trained on how to use an electronic daily diary to capture the following assessments: COPD-OEQ Daily, and rescue medication use. Additionally, the

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD-OEQ Weekly, PGIS, and Patient Global Impression of Change (PGIC) were captured offsite on Day 8. At the final visit, participants completed the COPD-OEQ Weekly, CAT, PGIS, and PGIC.

Analyses

Descriptive statistics were used to evaluate demographic characteristics and results from the COPD-OEQ and other measures of patient-reported outcomes. COPD-OEQ reproducibility between baseline and final visits was assessed using the phi coefficient, with the chi-square test of homogeneity used for statistical significance. Construct validity (convergent and known groups) examined the relationship between COPD-OEQ and spirometry results via post-dose percent change in FEV_1 (absolute value in milliliters) after administration of controller medication. Bronchodilator responsiveness was determined by a change of >12% and >200 mL in FEV_1 compared with baseline.[13] For convergent validity, a correlation coefficient of <0.3 was considered weak, 0.3 to 0.7 indicated moderate, 0.7 to 0.9 was considered strong, and >0.9 indicated very strong association.[14] Known-groups validity categorized participants by levels of disease severity, such as Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade based on FEV_1/FVC ratio <0.70 post-bronchodilator and post-bronchodilator FEV_1 % predicted, PEF, or PGIS, with COPD-OEQ scores (perception and satisfaction) higher for those with lower severity than for those with greater severity. Test-retest reliability of the COPD-OEQ Weekly and Daily was assessed between baseline and Day 8 and between baseline and the final visit (Day 14) among participants who reported "no change," as measured by PGIC and PGIS. Intraclass correlation (ICC) values >0.70 are generally considered acceptable for establishing test-retest reliability. For the secondary objective, the equivalence of the COPD-OEQ Weekly and Daily was evaluated by comparing the responses of the weekly with the distribution of the

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

daily responses. The equivalence of the weekly versus daily responses was assessed via a mixed model for repeated measures, with COPD-OEQ response predicted as a function of mode, time from the final visit (Day 14), and PGIS. It is expected that the regression coefficient for mode would include 0. As an exploratory objective, COPD-OEQ responses were evaluated by medication class at baseline. Classifications included LABA + LAMA, LAMA only, ICS + LABA, ICS + LABA + LAMA, and ICS + LABA combined with ICS + LABA + LAMA. Additional exploratory analyses evaluated the responses to the COPD-OEQ items by medication class and the correlations between COPD-OEQ weekly and daily items.

Results

Phase 1: Content Validity Qualitative Analysis

Patient characteristics

This analysis included 44 participants who were mostly female (54.5%) and White (88.6%) and had a mean age of 66.3 years (range: 47.0-82.0); the mean time since COPD diagnosis was 8 years (range: 1-24; **Table 1**). The symptom severity stratification, based on CAT scores, was as follows: <10 (n = 3), 11 to 20 (n = 17), 21 to 30 (n = 20), and >30 (n = 4). The medication groupings consisted of LAMA (n = 5; 11%), LABA + LAMA (n = 14; 32%), ICS + LABA (n = 10; 23%), ICS + LABA + LAMA (n = 10; 23%), and SABA alone (n = 5; 11%).

Concept Elicitation (CE)

Most participants (75%) reported being able to feel their medication working, using phrases such as “breathing better/easier,” “chest feeling less tight/heavy,” and “feeling airways opening up.” The timing of when participants first felt their medication begin to work varied from <1 minute

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

to ≥21 minutes, with most participants (62.5%) reporting that their medication started working in <21 minutes (**Figure 1**).

Cognitive Interviewing (CI)

Three OEQ items were determined to be relevant to the COPD population and understood as intended (OEQ Items 1, 2, and 5; **Table 2**). The content validity of 2 OEQ items was not supported (OEQ Items 3 and 4; **Table 2**). Based on findings from this qualitative analysis, OEQ Items 3 and 4 were not included in the subsequent quantitative analysis. Of note, the OEQ was designed to score each question individually, and does not result in a comprehensive score. Therefore, proceeding with 3 of 5 items did not impact the validity or reliability of the questionnaire.

Phase 2: Psychometric Properties Quantitative Analysis

Ninety-seven participants were included in the quantitative analysis. Participants were mostly female (57.7%) and White (92.8%), and the mean age was 71.3 years (range: 53.0-86.0; **Supplementary Table S1**). At baseline, most participants somewhat or strongly agreed with the COPD-OEQ Weekly assessment questions: 70.1% for OEQ Item 1, 59.8% for OEQ Item 2, and 60.8% for OEQ Item 5. For the COPD-OEQ Daily assessment, more than half of the participants somewhat or strongly agreed with OEQ Items 1, 2, and 5 for the duration of the analysis (**Figure 2**). Participants' lung function assessment at baseline is shown in **Table 3**.

Convergent validity

At the start of the study, it was hypothesized that the COPD-OEQ Weekly would have moderate to strong correlations with the PGIS and CAT, as well as moderate correlations with C-PPAC and FEV_1. Additionally, weak correlations were expected with morning and evening PEF and

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

FVC. During the study, moderate correlations were observed for the COPD-OEQ Weekly with PGIS at the final visit for COPD-OEQ Item 5 ([satisfied]: –0.36; p <0.05) and with C-PPAC at the final visit for all COPD-OEQ items (Item 1 [working]: 0.30; Item 2 [working right away]: 0.32; Item 5 [satisfied]: 0.35; all p <0.05). Moderate correlations were observed for COPD-OEQ Weekly Item 1 with FEV_1 pre-dose and FVC pre-dose (Item 1 [working]: –0.32 and –0.34, respectively; both p <0.05), for COPD-OEQ Weekly Item 2 with FVC pre-dose (Item 2 [working right away]: –0.31, p <0.05), and for COPD-OEQ Weekly Items 1 and 2 with FEV_1 post-dose (Item 1 [working] and Item 2 [working right away]: both –0.30, p <0.05) and FVC post-dose (Item 1 [working]: –0.33; Item 2 [working right away]: –0.34, both p <0.05).

For the COPD-OEQ Daily, it was expected that there would be moderate to strong correlations with the PGIS, moderate correlations with the C-PPAC, and weak correlations with the morning and evening PEF. Overall, for the COPD-OEQ Daily, weak correlations (<0.3) were observed for the CAT (all items p >0.05), PGIS (Item 5 only, p <0.05), and C-PPAC (all items p <0.05). Some moderate correlations were observed with FEV_1 pre-dose (Item 5 [satisfied]: –0.36, p <0.05), and FVC pre-dose (Item 5 [satisfied]: –0.39, p <0.05). Additionally, moderate correlations were observed for FEV1 post-dose (Item 5 [satisfied]: –0.33, p <0.05) and FVC post-dose (Item 5 [satisfied]: –0.38, p <0.05). Although minimal, moderate correlations were also detected with morning PEF change (Item 2 [working right away] Day 2: –0.34, Day 11: –0.31; Item 5 [satisfied] Day 2: –0.31, Day 8: –0.36, all p <0.05).

Known-groups validity

For the COPD-OEQ Weekly conducted at baseline, there were no significant differences between groups for PGIS or FEV_1, defined by a 12% improvement (**Supplementary Table S2**). Similarly, at Day 2, COPD-OEQ Items 1, 2, and 5 for morning maximum PEF and COPD-OEQ

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Item 5 for evening maximum PEF were not significant between groups (P >0.05); COPD-OEQ Items 1 and 2 were able to discriminate between patient groups for weekly evening maximum PEF (P = 0.04 and 0.01, respectively).

For the COPD-OEQ Daily conducted at baseline, there were no significant differences between groups for PGIS or >12% improvement in FEV_1 for OEQ Items 1 and 2. COPD-OEQ Daily Item 5 conducted at baseline for a >12% improvement in FEV_1 was able to discriminate participants in the expected direction (P = 0.04). With the COPD-OEQ Daily conducted at Day 2, morning maximum PEF was not significant between known groups (OEQ Item 1: P = 0.06; OEQ Item 2: P = 0.07; OEQ Item 5: P = 0.19). However, evening maximum PEF was significant between groups for OEQ Items 1, 2, and 5 (OEQ Item 1: P < 0.01; OEQ Item 2: P = 0.01; OEQ Item 5: P = 0.02) but in an unexpected order.

Test-retest reliability

For the COPD-OEQ Weekly measured on Day 8, P values were not significant (P = 0.10-0.42 and ICC values were generally moderate, ranging from 0.54 to 0.68. Similarly, for the COPD-OEQ Daily measured on Day 8, P values were not significant (P = 0.07-0.62) and ICC values were moderate (0.63-0.73). COPD-OEQ Item 5 had a high correlation (0.73).

Secondary and exploratory objective findings

There were no differences between participant responses on the COPD-OEQ Weekly recall and COPD-OEQ Daily recall assessments (odds ratio, 1.11; 95% confidence interval, 0.94-1.31; P = 0.21). As an exploratory objective, responses were evaluated by medication class. For COPD-OEQ Weekly, a greater proportion of participants with ICS-included medication at baseline strongly or somewhat agreed with the OEQ items (OEQ Item 1: 78.8%; OEQ Item 2: 66.7%;

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

OEQ Item 5: 66.7%) compared with those without ICS (**Supplementary Table S3**). Similar results were observed with the COPD-OEQ Daily (OEQ Item 1: 87.7%; OEQ Item 2: 73.8%; OEQ Item 5: 72.3%). For both the COPD-OEQ Weekly and Daily, OEQ Items 1, 2, and 5 were highly and significantly correlated with each other (all P <0.0001; data not shown).

Discussion

This study evaluated the content validity and psychometric properties of the OEQ in participants with mild to very severe COPD. The statements and responses assessed in the COPD-OEQ were the same as those measured in the Asthma-OEQ. In our qualitative analysis, the content validity of 3 OEQ items (Items 1, 2, and 5) was supported among participants with COPD, meaning these OEQ items (Items 1, 2, and 5) were found to be relevant, understood as intended, and able to be completed without difficulty. In the quantitative analysis of psychometric properties of the OEQ in participants with COPD, inconsistencies were found in the validity measures of the COPD-OEQ Weekly and Daily in this analysis population. In general, convergent validity tests resulted in weak correlations between the COPD-OEQ Weekly or COPD-OEQ Daily and CAT, PGIS, and C-PPAC. However, some questions in the COPD-OEQ Weekly had moderate correlations with FEV_1 and FVC. Similarly, the known-groups validity analysis suggested that neither the COPD-OEQ Weekly nor Daily instrument was able to discriminate subjects in the expected direction when comparing by PGIS, FEV_1, or morning or evening PEF. Test-retest reliability was generally moderate, with high ICC for OEQ Item 5.

The current results are not as striking as the strong reliability and validity seen with the OEQ in patients with asthma[11]; however, these results may be explained by looking at the pathophysiology of COPD compared with asthma. Despite the clear similarities between COPD and asthma, these diseases feature distinct types of airway inflammation and mediators, resulting

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

in differential response to therapy.[15,16] Asthma is characterized by more variability in airflow limitation compared with COPD and therefore may be more responsive to controller medications shortly after use.[17] Thus, the magnitude of lung function change is higher in asthma than in COPD. Furthermore, patients with COPD may be less likely to perceive airway limitations than patients with asthma due to adaptations in physical activity levels with COPD.[2] Therefore, patients with COPD may be less likely to perceive a notable effect of their medication. Lower baseline lung function tended to be associated with higher satisfaction. In general, lower baseline lung function increases the likelihood that small changes will correlate with patients feeling the onset of medication effects. However, in some cases, reduction of hyperinflation and dynamic hyperinflation by bronchodilators may improve FVC as much as, or more than, FEV_1. Therefore, unlike asthma, the correlation between lung function, bronchodilator responsiveness, and COPD-OEQ responses may not be as linear. Due to these clinical and non-clinical differences between asthma and COPD,[16] the trends in this analysis are consistent with the expectations for response to medication in patients with COPD compared with asthma.

Regarding similarity between daily and weekly recall, results confirmed that patients respond similarly to the COPD-OEQ items from the daily and weekly versions of the questionnaire. Comparable findings were also observed in the OEQ administered to patients with asthma.[11] However, given the possibility of questionnaire fatigue, the COPD-OEQ Daily may be considered redundant.

It was also observed that a greater proportion of patients using ICS/LABA-containing medications had an improved onset of effect (i.e., somewhat agreed and strongly agreed with the individual COPD-OEQ items). This could be due to the synergistic effect between corticosteroids and beta-agonist medications, in which corticosteroids enhance the

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

bronchodilatory effect of beta-agonists, and beta-agonists boost the anti-inflammatory response of corticosteroids.[18] Because patients do not all respond to the same medication, future investigations may be considered to expand the evaluation of the COPD-OEQ in subpopulations according to medication type.

Results reflecting differences between subgroup stratifications should be interpreted with caution due to small sample sizes and the recruitment of a convenience-based sample. Also because of small sample sizes, it was not feasible to include subanalyses on patients of different races, smoking status, and comorbidities. Due to clinical study recruiting challenges, demographic diversity in this study is limited; results may not be representative of the overall patient population. For example, the mean patient age in the current study is 71.3 years; responses from younger patients may differ from the current results. Additionally, other clinical subanalyses could have been performed had the OEQ proven to be more robust. Furthermore, a placebo comparator in future studies may assess the possibility of the placebo effect on patient-reported length of time to medication effect. Future studies are warranted to examine a more diverse patient population and to determine how this questionnaire may be used in future clinical studies.

Although there is content validity support for the assessment of perceived onset of effect in patients with COPD, the quantitative analyses of the COPD-OEQ Weekly and Daily provided weak evidence that the COPD-OEQ is a fit-for-purpose, reliable, valid, and well-defined measure for use in patients with moderate to severe COPD. Consequently, this tool is not ready for use in COPD populations at this time. The content validity of COPD-OEQ Items 1, 2, and 5 was supported among patients with COPD, demonstrating that these COPD-OEQ items are relevant, understood, and able to be completed without difficulty. Future studies are necessary to determine if the COPD-OEQ is a reliable and valid tool in targeted subsets of patients with

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD when endotype-specific studies emerge. In particular, one population that should be further studied includes those who currently require an ICS medication for COPD control.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Acknowledgments: All authors were involved in conceptuliazation and/or design of the study. NF and HG were involved in funding acquisition. GH and DR were involved with data analysis and interpretation. All authors were involved in writing and revision prior to submission. Medical writing support was provided by Kiley Margolis, PharmD, of Lumanity Communications Inc. under the direction of the authors in accordance with Good Publication Practice guidelines (GPP 2022) and was funded by AstraZeneca (Wilmington, DE, USA).

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Declaration of Interest: CS is a paid consultant to AstraZeneca, Bronchus, Morair, and PulManage; and received COPD research grants paid to the Medical University of South Carolina from CSA Medical, Renovion, and Nuvaira in COPD. BJM has received consulting fees from Optimum Patient Care Global Limited, Third Pole, and Verona; royalties from Wolters Kluwer Health (UpToDate); grants and contracts from NHLBI, American Lung Association, and Department of Defense; and reports participation on data safety monitoring boards for Baystate Medical Center, Mount Sinai, and Spiration; he serves on medical advisory boards for GlaxoSmithKline, Boehringer Ingelheim, and AstraZeneca; and as received compensation for CME activity from American College of Chest Physicians, Eastern Pulmonary Society, Mt. Sinai, Pri-Med, and WebMD. FJT, JME, NF, and HNG are employees of AstraZeneca. GH and DR are employees of Evidera, which was contracted by AstraZeneca for study design and to collect and analyze data for this study.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Data Sharing:

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

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Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table 1. Qualitative Analysis - Participant Demographics

Characteristic	Overall (n = 44)
Age, years[a]	
Mean (SD)	66.3 (9.3)
Range (min-max)	(47.0-82.0)
Sex, n (%)	
Male	20 (45.5)
Female	24 (54.5)
Ethnicity,[b] n (%)	
Not Hispanic or Latino	44 (100)
Race, ordered by frequency,[c] n (%)	
White	39 (88.6)
Black or African American	4 (9.1)
Other[b]	1 (2.3)
Living/domestic situation, n (%)	
With spouse, partner, or family friends	30 (68.2)
Alone	14 (31.8)

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Characteristic	Overall (n = 44)
Employment status,[a] n (%)	
Full time	6 (13.6)
Part time	8 (18.2)
Unemployed	1 (2.3)
Retired	17 (38.6)
Disabled	9 (20.5)
Other[d]	3 (6.8)
Education level,[c] n (%)	
Less than high school	2 (4.5)
Secondary/high school	16 (36.4)
Associate degree, technical or trade school	11 (25.0)
College/university degree	9 (20.5)
Post-graduate degree	2 (4.5)
Other[e]	4 (9.1)
Smoking status, n (%)	
Ex-smoker	28 (63.6)

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Characteristic	Overall (n = 44)
Current smoker	13 (29.5)
Never smoked	3 (6.8)
Overall health, n (%)	
Very good	3 (6.8)
Good	18 (40.9)
Fair	18 (40.9)
Poor	5 (11.4)
Time since diagnosis, years	
Mean (SD)	8 (5.9)
Range (min-max)	(1-24)
COPD severity by spirometric GOLD classification, n (%)	
Mild	3 (6.8)
Moderate	28 (63.6)
Severe	7 (15.9)
Very severe	3 (6.8)

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Characteristic	Overall (n = 44)
Missing	3 (6.8)
Hospitalizations in the past week, n (%)	
No	41 (93.2)
Yes	3 (6.8)

[a]One participant did not enter their age on the sociodemographic form; the age for this participant was based on the enrollment log.

[b]Not mutually exclusive.

[c]Other: American Indian or Alaska Native and White.

[d]Other: "Retired and disabled" (n = 2) and "Retired with painting job" (n = 1).

[e]Other: "Some college" (n = 3). One participant selected "Other" for education; however, the handwritten specification was illegible.

SD, standard deviation; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table 2. Content Validity of the OEQ in COPD: Item-level Assessment

OEQ item	CI results		Item determined to be relevant to the COPD population and understood as intended
	Understood item as intended	Indicated item was important to ask[a]	
OEQ Item 1. During the past week, you could tell your study medication was working	95% (n = 42/44)	98% (n = 41/42)	**Supported**
OEQ Item 2. During the past week, you could feel your study medication begin to work right away	93% (n = 41/44)	95% (n = 38/40)	**Supported**
OEQ Item 3. During the past week, you felt physical sensations shortly after taking your study medication that reassured you that it was working	98% (n = 43/44)	93% (n = 37/40)	**Not supported** Descriptions varied and were not always aligned with the intention of the item; therefore, the item was deemed not relevant due to participants being unable to provide consistent or clear physical

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

			sensations related to their medication working
OEQ Item 4. During the past week, your study medication worked as quickly as your albuterol	82% (n = 36/44)	74% (n = 28/38)	**Not supported** Item was not clearly understood; most issues centered around the comparison to albuterol
OEQ Item 5. During the past week, you were satisfied with how quickly you felt your study medication begin to work	100% (n = 44/44)	98% (n = 39/40)	**Supported**

[a]Due to the nature of qualitative interviews and to avoid participant fatigue and burden, not all participants were asked all questions in the semi-structured interview guide.

OEQ, Onset of Effect Questionnaire; COPD, chronic obstructive pulmonary disease; CI, cognitive interviewing.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table 3. Qualitative Analysis - Lung Function Assessment at Baseline

Measure	n	Mean	SD	Median	IQR (P25-P75)	Range (min-max)
Pre-dose at baseline						
FEV_1, mL	97	1237.8	421.0	1210.0	610.0 (900.0-1510.0)	(570.0-2669.0)
FVC, mL	97	2420.7	739.2	2270.0	910.0 (1970.0-2880.0)	(1150.0-5031.0)
IC, L	89	2.0	0.6	1.9	0.8 (1.6-2.4)	(1.1-3.5)
Peak IC, L/sec	87	2.1	0.9	2.0	1.4 (1.4-2.8)	(0.7-4.5)
PEF, L/sec	97	3.6	1.3	3.5	2.1 (2.4-4.5)	(1.4-7.7)
Post-dose at baseline						
FEV_1, mL	96	1351.8	442.0	1315.0	615.0 (1005.0-1620.0)	(600.0-2751.0)
FVC, mL	96	2580.9	765.9	2475.0	1045.0 (2070.0-3115.0)	(1180.0-4800.0)
Peak IC, L/sec	90	2.4	1.0	2.2	1.3 (1.7-2.9)	(0.5-5.5)
PEF, L/sec	96	3.8	1.4	3.5	1.9 (2.7-4.6)	(1.3-8.6)
Change (post-dose at baseline – pre-dose at baseline)[a]						
FEV_1, mL	96	110.9	137.3	100.0	145.0 (20.0-165.0)	(–220.0-600.0)
FVC, mL	96	157.7	222.4	140.0	230.0 (25.0-255.0)	(–380.0-1140.0)

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

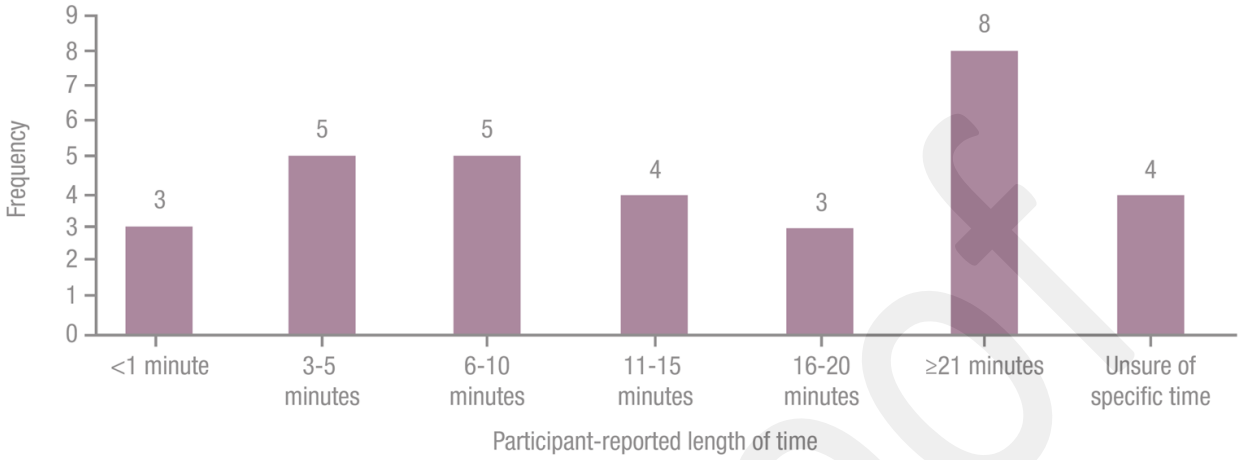
Measure	n	Mean	SD	Median	IQR (P25-P75)	Range (min-max)
Peak IC, L/sec	86	0.3	0.6	0.2	0.6 (0.0-0.5)	(–1.8-3.1)
PEF, L/sec	96	0.2	0.6	0.2	0.7 (–0.1-0.6)	(–3.3-1.5)

[a]Simple subtraction may not apply due to differences in sample size.

SD, standard deviation; IQR, interquartile range; P, period; FEV_1, forced expiratory volume in the first second; mL, milliliter; FVC, forced vital capacity; IC, inspiratory capacity; L, liter; sec, second; PEF, peak expiratory flow.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Figure 1. CE – Participant-reported Length of Time to Feel Medication Working[a,b]



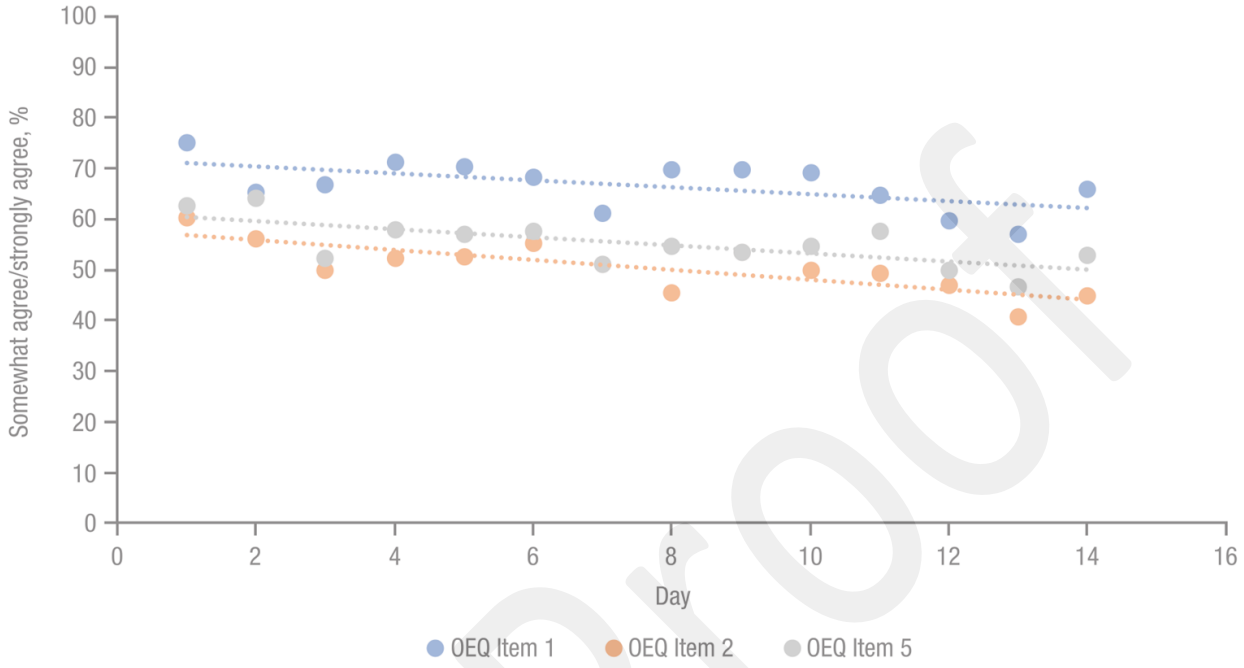
[a]Data reported from those respondents who reported that they could feel their medication working (n = 33). One participant was not asked or did not respond.

[b]Study medications included fluticasone propionate/salmeterol; umeclidinium bromide/vilanterol; glycopyrrolate/formoterol fumarate; fluticasone furoate/vilanterol; ipratropium bromide/albuterol; albuterol; tiotropium bromide; tiotropium bromide/olodaterol; budesonide/formoterol; fluticasone furoate/umeclidinium/vilanterol.

CE, concept elicitation.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Figure 2. Dichotomized COPD-OEQ Daily Results for OEQ Items 1, 2, and 5 Over Time (Baseline to Final Visit)



COPD, chronic obstructive pulmonary disease; OEQ, Onset of Effect Questionnaire.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Online Supplement

The supplemental files are presented to further understand the heterogeneous COPD patient population used in this study. Correlation with Peak Expiratory Flow values are shown. Questionnaires that were specified by the study protocol, but for which data are not shown, include the following: Nighttime Symptoms of COPD Instrument (NiSCI), Exacerbations of Chronic Obstructive Pulmonary Disease Tool – Patient-Reported Outcomes (EXACT-PRO, and PROactive Physical Activity in COPD (C-PPAC).

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table S1. Quantitative Analysis - Participant Demographics

Characteristic	Overall (n = 97)
Age, years	
Mean (SD)	71.3 (7.0)
Median	72.0
Range (min-max)	(53.0-86.0)
IQR (P25-P75)	9.0 (67.0-76.0)
Sex, n (%)	
Male	41 (42.3)
Female	56 (57.7)
Ethnicity, n (%)	
Hispanic or Latino	2 (2.1)
Not Hispanic or Latino	95 (97.9)
Race, ordered by frequency,[a] n (%)	
Indian	1 (1.0)
Black	7 (7.2)
White	90 (92.8)

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Characteristic	Overall (n = 97)
Marital status, n (%)	
Single	18 (18.6)
Married	37 (38.1)
Divorced	24 (24.7)
Widowed	16 (16.5)
Other	2 (2.1)
Smoking status, n (%)	
Current	38 (39.2)
Previous	58 (59.8)
Never	1 (1.0)

[a]Not mutually exclusive as one individual reported more than one race.

SD, standard deviation; IQR, interquartile range; P, period.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table S2. Known-groups Validity for COPD-OEQ Weekly and Daily at Baseline

COPD-OEQ item	Measure	n	LSMean (SE)	*P* value
COPD-OEQ Weekly				
OEQ 1. You could tell your study medication was working	**PGIS**			0.3096
	None/mild	27	3.0 (0.2)	
	Moderate	55	2.8 (0.1)	
	Severe/very severe	14	3.3 (0.3)	
	FEV_1 improvement			0.4727
	<12%	60	2.9 (0.1)	
	≥12%	37	3.1 (0.2)	
	Morning maximum PEF[a]			0.8314
	Red zone: <200 LPM	43	3.0 (0.2)	
	Yellow zone: 200-320 LPM	23	2.9 (0.2)	
	Green zone: 320-400 LPM	12	3.0 (0.3)	
	Evening maximum PEF[a]			0.0377
	Red zone: <200 LPM	42	3.1 (0.1)	
	Yellow zone: 200-320 LPM	29	3.1 (0.2)	
	Green zone: 320-400 LPM	9	2.2 (0.3)	
	PGIS			0.3842

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD-OEQ item	Measure	n	LSMean (SE)	*P* value
OEQ 2. You could feel your study medication begin to work right away	None/mild	27	2.6 (0.2)	
	Moderate	55	2.4 (0.1)	
	Severe/very severe	14	2.9 (0.3)	
	FEV_1 improvement			0.9653
	<12%	60	2.6 (0.1)	
	≥12%	37	2.5 (0.2)	
	Morning maximum PEF[a]			0.1543
	Red zone: <200 LPM	43	2.6 (0.2)	
	Yellow zone: 200-320 LPM	23	2.4 (0.2)	
	Green zone: 320-400 LPM	12	2.0 (0.3)	
	Evening maximum PEF[a]			0.0111
	Red zone: <200 LPM	42	2.6 (0.2)	
	Yellow zone: 200-320 LPM	29	2.6 (0.2)	
	Green zone: 320-400 LPM	9	1.6 (0.3)	
OEQ 5. You were satisfied with how quickly you felt your study medication begin to work	**PGIS**			0.6145
	None/mild	27	2.9 (0.2)	
	Moderate	55	2.7 (0.1)	
	Severe/very severe	14	2.6 (0.3)	
	FEV_1 improvement			0.5384

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD-OEQ item	Measure	n	LSMean (SE)	*P* value
	<12%	60	2.7 (0.1)	
	≥12%	37	2.8 (0.2)	
	Morning maximum PEF[a]			0.5658
	Red zone: <200 LPM	43	2.8 (0.2)	
	Yellow zone: 200-320 LPM	23	2.7 (0.2)	
	Green zone: 320-400 LPM	12	2.4 (0.3)	
	Evening maximum PEF[a]			0.0652
	Red zone: <200 LPM	42	2.8 (0.1)	
	Yellow zone: 200-320 LPM	29	2.8 (0.2)	
	Green zone: 320-400 LPM	9	2.0 (0.3)	
COPD-OEQ Daily				
OEQ 1. You could tell your study medication was working	**PGIS**			0.1713
	None/mild	27	3.2 (0.2)	
	Moderate	55	2.8 (0.1)	
	Severe/very severe	13	3.3 (0.3)	
	FEV_1 improvement			0.2660
	<12%	60	2.9 (0.1)	
	≥12%	36	3.2 (0.2)	
	Morning maximum PEF[a]			0.0632

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD-OEQ item	Measure	n	LSMean (SE)	*P* value
	Red zone: <200 LPM	42	3.2 (0.2)	
	Yellow zone: 200-320 LPM	23	2.9 (0.2)	
	Green zone: 320-400 LPM	12	2.4 (0.3)	
	Evening maximum PEF[a]			0.0003
	Red zone: <200 LPM	41	3.2 (0.1)	
	Yellow zone: 200-320 LPM	29	3.1 (0.2)	
	Green zone: 320-400 LPM	9	1.8 (0.3)	
OEQ 2. You could feel your study medication begin to work right away	**PGIS**			0.3835
	None/mild	27	2.7 (0.2)	
	Moderate	55	2.5 (0.1)	
	Severe/very severe	13	2.8 (0.3)	
	FEV_1 improvement			0.0690
	<12%	60	2.5 (0.1)	
	≥12%	36	2.8 (0.2)	
	Morning maximum PEF[a]			0.0747
	Red zone: <200 LPM	42	2.8 (0.2)	
	Yellow zone: 200-320 LPM	23	2.3 (0.2)	
	Green zone: 320-400 LPM	12	2.2 (0.3)	
	Evening maximum PEF[a]			0.0104

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD-OEQ item	Measure	n	LSMean (SE)	*P* value
	Red zone: <200 LPM	41	2.8 (0.2)	
	Yellow zone: 200-320 LPM	29	2.4 (0.2)	
	Green zone: 320-400 LPM	9	1.7 (0.3)	
OEQ 5. You were satisfied with how quickly you felt your study medication begin to work	**PGIS**			0.7835
	None/mild	27	2.9 (0.2)	
	Moderate	55	2.8 (0.1)	
	Severe/very severe	13	2.8 (0.3)	
	FEV_1 improvement			0.0440
	<12%	60	2.7 (0.1)	
	≥12%	36	3.1 (0.2)	
	Morning maximum PEF[a]			0.1919
	Red zone: <200 LPM	42	3.0 (0.2)	
	Yellow zone: 200-320 LPM	23	2.5 (0.2)	
	Green zone: 320-400 LPM	12	2.7 (0.3)	
	Evening maximum PEF[a]			0.0253
	Red zone: <200 LPM	41	3.0 (0.2)	
	Yellow zone: 200-320 LPM	29	2.8 (0.2)	
	Green zone: 320-400 LPM	9	2.0 (0.3)	

[a]Morning and evening PEF starts on Day 2.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

COPD, chronic obstructive pulmonary disease; OEQ, Onset of Effect Questionnaire, LSMean, least squares mean; SE, standard error; PGIS, Patient Global Impression of COPD Severity; FEV_1, forced expiratory volume in the first second; PEF, peak expiratory flow; LPM, liters per minute.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

Table S3. COPD-OEQ Weekly and Daily – Dichotomized Response Distribution (%) at Baseline, by Medication Class

Characteristic, n (%)	Strongly disagree/somewhat disagree/neither agree nor disagree	Somewhat agree/strongly agree
COPD-OEQ Weekly		
OEQ 1. You could tell your study medication was working		
Non-ICS (LABA/LAMA + LAMA)	18 (50.0)	18 (50.0)
ICS (ICS/LABA + ICS/LABA/LAMA)	14 (21.2)	52 (78.8)
OEQ 2. You could feel your study medication begin to work right away		
Non-ICS (LABA/LAMA + LAMA)	19 (52.8)	17 (47.2)
ICS (ICS/LABA + ICS/LABA/LAMA)	22 (33.3)	44 (66.7)
OEQ 5. You were satisfied with how quickly you felt your study medication begin to work		
Non-ICS (LABA/LAMA + LAMA)	18 (50.0)	18 (50.0)
ICS (ICS/LABA + ICS/LABA/LAMA)	22 (33.3)	44 (66.7)
COPD-OEQ Daily		

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485

OEQ 1. You could tell your study medication was working		
Non-ICS (LABA/LAMA + LAMA)	17 (47.2)	19 (52.8)
ICS (ICS/LABA + ICS/LABA/LAMA)	8 (12.3)	57 (87.7)
OEQ 2. You could feel your study medication begin to work right away		
Non-ICS (LABA/LAMA + LAMA)	22 (61.1)	14 (38.9)
ICS (ICS/LABA + ICS/LABA/LAMA)	17 (26.2)	48 (73.8)
OEQ 5. You were satisfied with how quickly you felt your study medication begin to work		
Non-ICS (LABA/LAMA + LAMA)	20 (55.6)	16 (44.4)
ICS (ICS/LABA + ICS/LABA/LAMA)	18 (27.7)	47 (72.3)

COPD, chronic obstructive pulmonary disease; OEQ, Onset of Effect Questionnaire; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

Published online May 7, 2024 https://doi.org/10.15326/jcopdf.2023.0485