Capturing Exacerbations of Chronic Obstructive Pulmonary Disease with EXACT

A Subanalysis of FLAME

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Abstract

Rationale: Chronic obstructive pulmonary disease exacerbations accelerate lung function decline, reduce quality of life, and increase mortality. A subset of patients ($n = 457$) from the FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study used the Exacerbations of COPD Tool (EXACT) to capture symptom-defined exacerbations.

Objectives: To evaluate the effect of indacaterol/glycopyrronium versus salmeterol/fluticasone on symptom-defined exacerbations measured using EXACT, and to assess differences between these events and exacerbations requiring healthcare resource use (HCRU).

Methods: All patients in FLAME used an electronic diary to record and detect symptom deteriorations; HCRU-related exacerbations were confirmed by investigators. In patients using the EXACT questionnaire, the onset, recovery, and magnitude of symptom-defined exacerbations were identified by changes in total scores relative to baseline. We analyzed the annualized rate and time to first symptom-defined (EXACT) exacerbation and assessed differences between symptom-defined and HCRU events in terms of number, severity, and concordance.

Measurements and Main Results: A nonsignificant 17% reduction in the annualized rate of symptom-defined (EXACT) exacerbations (rate ratio, 0.83; 95% confidence interval [CI], 0.60–1.14; $P = 0.242$) and a numerically longer time to first symptom-defined exacerbation were observed with indacaterol/glycopyrronium versus salmeterol/fluticasone (hazard ratio, 0.76; 95% CI, 0.56–1.03; $P = 0.075$). These results were consistent with data from the overall FLAME population. Of the symptom-defined (EXACT) events, 23.5% corresponded to HCRU events, and 22.2% of HCRU events were captured by EXACT (κ index, 0.24; 95% CI, 0.15–0.33).

Conclusions: Regardless of the exacerbation definition used, our findings support the use of long-acting β_2 agonists/long-acting muscarinic receptor antagonists as the preferred treatment option for patients at risk of future exacerbations.

Clinical trial registered with www.clinicaltrials.gov (NCT01782326).

Keywords: defined symptom; exacerbation; concordance; treatment

Exacerbations of chronic obstructive pulmonary disease (COPD) are acute worsenings of symptoms that require changes in medication and/or hospitalization (1).

Exacerbations are associated with accelerated lung function decline (2–4), reduced quality of life/health status (4–6), and increased mortality (1, 4, 7).

The FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study demonstrated superiority of the long-acting β_2 agonist

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At a Glance Commentary

Scientific Knowledge on the

Subject: The FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study showed indacaterol/glycopyrronium (IND/GLY) to be superior to salmeterol/fluticasone (SFC) in reducing exacerbation rate and delaying time to first exacerbation requiring healthcare resource use; however, it is not known whether there is a difference between the two treatments on outcomes measured using the EXACT questionnaire.

What This Study Adds to the

Field: We evaluated the effects of IND/GLY versus SFC on symptom-defined exacerbations detected with EXACT in a subset of patients in FLAME and assessed differences between investigator-confirmed healthcare resource use exacerbations and symptom-defined (EXACT) exacerbations. Consistent with the findings from FLAME, IND/GLY provided numerical improvements in reducing the rate and prolonging the time to first symptom-defined (EXACT) exacerbation relative to SFC. Owing to the small sample size these improvements were not statistically significant.

(LABA)/long-acting muscarinic receptor antagonist (LAMA) combination of indacaterol/glycopyrronium (IND/GLY) versus the LABA/inhaled corticosteroid combination of salmeterol/fluticasone propionate (SFC) on COPD exacerbation prevention, irrespective of baseline blood eosinophil count (8, 9). The findings supported the Global Initiative for Chronic Obstructive Lung Disease 2017 recommendation of LABA/LAMA as the preferred treatment option for patients at higher risk of exacerbations (1).

COPD exacerbations have no universally established definition (10) and are subject to diagnostic uncertainty (11). Historically, exacerbations have been defined as events that required healthcare resource use (HCRU), with moderate exacerbations requiring administration of oral steroids and/or antibiotics and severe exacerbations

requiring hospitalization (10, 12–14). However, healthcare use in COPD varies widely depending on access, leading to disparities across different healthcare systems. Furthermore, HCRU definitions may not capture events unreported to healthcare professionals; such events comprise up to two-thirds of exacerbations (5, 15). Unreported exacerbations can impair health-related quality of life (5, 6, 15, 16) and increase the risk of hospitalization (17).

In the FLAME study, an electronic diary (e-diary) was the primary patient-reported outcome (PRO) instrument, which was used by all patients to record the severity of their daily COPD symptoms and alert patients to symptom deteriorations relative to baseline levels (18). An additional exploratory and prespecified objective was to assess the use of another PRO instrument, the Exacerbations of COPD Tool (EXACT) (19–21), as a means of capturing symptom-defined exacerbations in a subset of patients. The EXACT is a 14-item questionnaire designed to standardize the method for evaluating acute COPD exacerbations in clinical trials. The EXACT was developed and validated to measure symptom-defined exacerbations and provides information on the frequency, severity, and duration of exacerbation events (20–24). The purpose of this subanalysis of the FLAME study was to evaluate the effect of IND/GLY versus SFC on outcomes measured using an electronic form of the EXACT questionnaire, and to assess differences between physician-confirmed exacerbations requiring HCRU and symptom-defined exacerbations using the EXACT. Some of the results of this analysis have been reported previously in abstract form (25–27).

Methods

Study Design

The design and conduct of the FLAME study (NCT01782326) has been reported previously (8). Patients with COPD and a history of at least one exacerbation during the previous year were randomized 1:1 to receive either once-daily IND/GLY (110/50 µg) or twice-daily SFC (50/500 µg). The primary outcome was the annual rate of all COPD exacerbations.

EXACT Analysis Population

The EXACT analysis population comprised a subset of patients from the FLAME full

analysis set (FAS). According to the study protocol, the EXACT questionnaire was to be completed by a subset of ~500 patients, in countries where validated translations were available. This analysis included patients in FAS, who provided an additional informed consent for participation in the EXACT substudy. Only patients with a baseline EXACT total score who had at least 2 consecutive days with a postbaseline EXACT total score were included in the EXACT set.

Assessment and Definition of COPD Exacerbations

Protocol-defined exacerbations were identified from the e-diary data as a worsening of symptoms according to Anthonisen and colleagues (28) criteria relative to baseline levels obtained during the run-in period. Patients were alerted by the e-diary to a worsening of symptoms; however, the investigator had to confirm the exacerbation and recommend additional treatment (i.e., antibiotics and/or systemic corticosteroids) as appropriate. Treated events were recorded on an electronic case report form (eCRF) as moderate or severe exacerbations (i.e., moderate exacerbations were those requiring systemic corticosteroids and/or antibiotics, and severe events were those requiring hospitalization). For the purpose of reporting in this study, these moderate/severe exacerbations are subsequently described as HCRU exacerbations.

Using the EXACT questionnaire, the onset, recovery, and magnitude of a symptom-defined exacerbation were identified by changes in the EXACT total score relative to baseline values. The EXACT total score is the sum of the raw score of all 14 questions and has a range of 0 to 100, with higher scores indicating greater severity. The onset of an EXACT event was defined as a sustained worsening of EXACT daily score of ≥ 12 points above baseline values during 2 consecutive days or of ≥ 9 points during 3 consecutive days, with Day 1 of the symptom worsening serving as Day 1 (onset) of the event (21, 29). Recovery was characterized by an improvement of at least 9 points from the maximum value of the EXACT total score during the event, sustained for 7 days using a 3-day rolling average, with the first day designated the day of recovery. The duration of the event was defined as the number of days from onset to recovery of the event, whereas the severity of an EXACT event was defined as the maximum EXACT total score during the event.

A symptom-defined (EXACT) exacerbation was considered reported when at least 1 day of the event corresponded to the start date $\pm$ 7 days of an HCRU exacerbation. Conversely, HCRU exacerbations were considered captured with EXACT when at least 1 day of the exacerbation, as recorded on the eCRF, corresponded to the start date $\pm$ 7 days of a symptom-defined exacerbation.

Additional details on EXACT scoring and the use of each PRO tool are provided in the online data supplement.

Statistical Analyses

The annual rate of exacerbations was analyzed using a generalized linear model with a negative binomial distribution (*see* online supplement for further details on statistical issues and analysis methods).

Time to first exacerbation was analyzed using a Cox proportional hazard model. A log rank test (unstratified) was performed to examine the between-group treatment difference.

The percentage of days on a symptom-defined exacerbation for an individual patient was defined as the ratio of the total number of days with the exacerbation as captured by the EXACT tool and the time the patient was exposed to study treatment

and completed the EXACT questionnaire; these were summarized descriptively by treatment groups. The EXACT severity was also summarized for HCRU exacerbations and symptom-defined (EXACT) events.

An analysis of the percentage of days without exacerbations was conducted using a linear mixed model, as was an analysis of the EXACT severity of the worst symptom-defined (EXACT) or HCRU exacerbations.

An analysis of the likelihood of future moderate/severe exacerbations on the basis of previous symptom-defined (EXACT) events (EXACT subset) was performed using a generalized linear model with a negative binomial distribution.

The total number of exacerbations captured with EXACT within each patient were compared with the total number of HCRU exacerbations using the Wilcoxon signed-rank test. In addition, the κ index was calculated to assess the agreement between the EXACT instrument and HCRU methods to detect exacerbations.

All analyses were conducted using the statistical software SAS versions 9.3 or 9.4.

Results

The EXACT subset comprised 457 patients from the 3,362 patients randomized to the

FLAME study. Four patients were excluded from the analysis due to insufficient data or protocol deviations. The analysis population therefore comprised 453 patients, representing 13.5% of the FLAME population. Of these, 233 were randomized to IND/GLY and 220 to SFC (*see* online supplement for further details).

During the study, high completion rates of the EXACT questionnaire were observed in both treatment arms (mean compliance rates of 91.0% and 93.6% in the IND/GLY and SFC treatment arms, respectively).

Demographic and Baseline Characteristics

Baseline characteristics of the EXACT subset are shown in Table 1 alongside those of the FAS. Comparisons are also shown of patients included versus not included in the EXACT subset. The EXACT subgroup was younger, had a greater proportion of female participants, a longer duration of COPD, a higher proportion of current smokers, and greater baseline FEV₁ and COPD Assessment Test (CAT) scores than patients not included in the EXACT subset.

Description of Symptom-defined (EXACT) Exacerbations

A total of 80 and 89 patients in the IND/GLY and SFC treatment groups

Table 1. Baseline Characteristics of the Patients in the EXACT Subset by Treatment Group and Comparison of EXACT versus Non-EXACT Patients in FLAME

Characteristic	EXACT Subset (N = 453)		EXACT (N = 453)	Non-EXACT (N = 2,909)	P Value*
	IND/GLY (n = 233)	SFC (n = 220)			
Age, yr, mean $\pm$ SD	63.6 $\pm$ 7.4	62.3 $\pm$ 7.7	63.0 $\pm$ 7.6	64.8 $\pm$ 7.8	<0.001
Male, n (%)	151 (64.8)	143 (65.0)	294 (64.9)	2,263 (77.8)	<0.001
Duration of COPD, yr, mean $\pm$ SD	8.7 $\pm$ 6.2	8.3 $\pm$ 5.5	8.5 $\pm$ 5.9	7.1 $\pm$ 5.3	<0.001
ICS use at screening, n (%)	135 (57.9)	122 (55.5)	257 (56.7)	1,636 (56.2)	0.84
Current smoker, n (%)	112 (48.1)	110 (50.0)	222 (49.0)	1,111 (38.2)	<0.001
Severity of COPD, [†] n (%)					0.13
Group A	1 (0.4)	0	—	—	
Group B	69 (29.6)	56 (25.5)	—	—	
Group C	0	0	—	—	
Group D	161 (69.1)	164 (74.5)	—	—	
Post-bronchodilator FEV ₁ , [‡] L, mean $\pm$ SD	1.26 $\pm$ 0.4	1.29 $\pm$ 0.4	1.3 $\pm$ 0.4	1.2 $\pm$ 0.3	<0.001
Post-bronchodilator FEV ₁ , [‡] % predicted $\pm$ SD	44.6 $\pm$ 9.7	44.7 $\pm$ 8.9	44.7 $\pm$ 9.3	44.0 $\pm$ 9.5	0.15
Post-bronchodilator FEV ₁ /FVC, [‡] % $\pm$ SD	42.0 $\pm$ 9.8	41.5 $\pm$ 9.7	41.8 $\pm$ 9.8	41.5 $\pm$ 9.9	0.67
CAT score, [§] mean $\pm$ SD	17.7 $\pm$ 7.0	17.8 $\pm$ 6.7	17.7 $\pm$ 6.8	16.6 $\pm$ 7.0	0.001

Definition of abbreviations: CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; EXACT = Exacerbations of COPD Tool; FLAME = Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations; ICS = inhaled corticosteroid; IND/GLY = indacaterol/glycopyrronium; SFC = salmeterol/fluticasone propionate.

*Difference between EXACT versus non-EXACT patients for baseline characteristics.

[†]As reflected in the 2015 version of the Global Initiative for Chronic Obstructive Lung Disease guidelines.

[‡]At screening.

[§]On a scale of 0–40, higher scores indicate worse health status.

experienced a total of 137 and 148 symptom-defined (EXACT) exacerbations, respectively; mean (SD) number per patient of 0.6 (1.0) and 0.7 (1.2) (Table 2). In patients who experienced symptom-defined exacerbations, the mean number of reported events was 0.4 per patient in both treatment arms (SD 0.6 for IND/GLY, 0.5 for SFC); the mean number of unreported events was 1.3 per patient in both treatment arms (SD 1.0 and 1.3, respectively).

The mean percentage of days with COPD exacerbations assessed using EXACT was lower in patients treated with IND/GLY than with SFC (7% vs. 9%, $P = 0.38$); likewise, the mean (SD) total number of days with symptom-defined (EXACT) exacerbations was lower with IND/GLY versus SFC (36 [46.40] vs. 42 [51.42] d, $P = 0.45$; Table 2). Patients treated with IND/GLY also experienced a higher percentage of days without symptom-defined exacerbations than did SFC-treated patients (93% vs. 91%; $P = 0.36$) and a higher percentage of days without symptom-defined or HCRU exacerbations (89% vs. 86%; $P = 0.13$), although these differences were not statistically significant (Table 2).

Analysis of Symptom-defined (EXACT) Exacerbations in the IND/GLY versus SFC Groups: EXACT Subset

The annualized rate of symptom-defined exacerbations using the EXACT was numerically lower with IND/GLY compared with SFC (0.85 vs. 1.03 events/patient/yr). During the 52-week treatment period this equated to a 17% reduction in exacerbation rate with IND/GLY versus SFC, which did not reach statistical significance (rate ratio, 0.83; 95% confidence interval [CI], 0.60–1.14; $P = 0.24$) (Figure 1 and Table 3). Similar results were observed in most EXACT patient subgroups analyzed, with fewer exacerbations observed in the IND/GLY arm compared with the SFC arm (see Figure E1 in the online supplement). The annualized rate of unreported symptom-defined (EXACT) exacerbations was also lower with IND/GLY versus SFC (rate ratio, 0.81; 95% CI, 0.57–1.16; $P = 0.25$) (Table 3). IND/GLY prolonged the time to the first symptom-defined (EXACT) exacerbation, providing a numerical but not statistically significant delay of 24% in the time to first exacerbation compared with SFC (hazard

ratio, 0.76; 95% CI, 0.56–1.03; $P = 0.08$; Figure 1 and Figure E2).

Comparative Data of Symptom-defined (EXACT) and HCRU Exacerbations

The ability of the EXACT to capture the frequency of exacerbations was compared with HCRU exacerbation frequency as recorded on the eCRF. The number of HCRU events was higher than the symptom-defined events using the EXACT; however, the difference was not significant (Table E1). Of all events captured by EXACT, 23.5% (67 of 285) corresponded to HCRU events. Conversely, only 22.2% (70 of 316) of all HCRU events were captured with the EXACT tool. The κ index of concordance between the two methods was 0.24 (95% CI, 0.15–0.33) (Table 2).

Series plots of mean EXACT total scores 14 days before the onset of the first reported and unreported symptom-defined (EXACT) events until 28 days after onset are shown in Figure 2 alongside a similar plot showing mean EXACT total scores during the first HCRU exacerbations. Baseline scores (i.e., in the 14 d prior to the onset of the first EXACT event) were found to be higher in reported versus unreported symptom-defined (EXACT) events. In addition, reported symptom-defined (EXACT) events were of greater severity than unreported events, with the maximum score of the latter being of similar magnitude to HCRU events. The mean increase in the EXACT total score during the first HCRU exacerbations was far below the threshold for a symptom-defined (EXACT) event.

Comparison of EXACT Scores by Treatment Group to Assess Severity of Exacerbation

The severity of symptom-defined (EXACT) events was similar between the treatment arms, as was the EXACT severity and mean EXACT total scores during HCRU exacerbations (Table 2). An analysis confirmed that there were no between-treatment differences in adjusted EXACT severity of the worst exacerbations whether symptom defined (EXACT) or protocol defined (data not shown).

Predictive Value of Exacerbations Captured with the EXACT Tool

We conducted an analysis to assess whether exacerbations identified using EXACT were

capable of predicting future exacerbations. Symptom-defined (EXACT) exacerbations that occurred during the first 12 weeks of treatment were found to be associated with a higher, although not statistically significant, risk of the occurrence of subsequent moderate or severe exacerbations (HCRU) during the remaining double-blind treatment period (Table 4).

Discussion

In this prespecified analysis of the FLAME study we have shown that IND/GLY provides numerical but not statistically significant improvements versus SFC in reducing and delaying symptom-defined exacerbations using the EXACT. The lack of statistical significance during the treatment period, however, is likely to be related to the small sample size of the EXACT subset ($N = 453$; 13.5% of the FLAME population), which was insufficient to provide statistical power to compare the differences between the two drugs in the reduction of exacerbations. For both outcome measures, the point estimates for the rate ratios of the comparisons were of similar magnitude to the findings obtained in the FAS of the FLAME study (8). Hence, in FLAME, significant reductions of 12% and 17%, respectively, in all-severity and HCRU exacerbations were observed with IND/GLY versus SFC, whereas in the EXACT subset a similar 17% reduction relative to SFC was observed, although this was not statistically significant (Figure E2). IND/GLY also significantly prolonged time to first exacerbation relative to SFC in FLAME by 16% for all-severity exacerbations and by 22% for HCRU events. A delay of 24% in the time to first symptom-defined (EXACT) event was observed in the IND/GLY arm compared with SFC treatment arm, although again this difference was not statistically significant (Figure E2). As evidenced from the Forest plots, the confidence intervals in the EXACT analyses are much wider due to the much smaller sample size. In support of the primary analysis result, IND/GLY was also associated with a numerically higher percentage, albeit not statistically significant, of symptom-defined exacerbation-free days than in SFC-treated patients.

Because a considerable proportion of exacerbations remains unreported (5, 6, 15, 16),

Table 2. Summary of Symptom-defined (EXACT) and Healthcare Resource Use Exacerbations in the EXACT Subset during 52 Weeks

Variable	IND/GLY (n = 233)	SFC (n = 220)
Total number of symptom-defined (EXACT) exacerbation episodes	137	148
Average number of treatment years*	0.89	0.84
Occurrence rate in 100 patient-years	66.14	79.82
Number (%) of patients with symptom-defined (EXACT) exacerbations	80 (34.3)	89 (40.5)
Number of symptom-defined (EXACT) exacerbations per patient		
Mean (SD)	0.6 (1.0)	0.7 (1.2)
Range	0 to 6	0 to 8
Number (%) of patients with symptom-defined (EXACT) events by number category		
0	153 (65.7)	131 (59.5)
1	42 (18.0)	57 (25.9)
2	28 (12.0)	21 (9.5)
3	5 (2.1)	5 (2.3)
≥4	5 (2.1)	6 (2.7)
Number of reported symptom-defined (EXACT) exacerbations per patient		
Mean (SD)	0.4 (0.6)	0.4 (0.5)
Number of unreported symptom-defined (EXACT) exacerbations per patient		
Mean (SD)	1.3 (1.0)	1.3 (1.3)
Number of days with symptom-defined (EXACT) exacerbation per patient		
Mean (SD)	35.9 (46.4)	41.9 (51.4)
Percentage of days with symptom-defined (EXACT) exacerbation per patient		
Mean (SD)	7.4 (17.9)	8.9 (18.2)
Percentage of days without symptom-defined (EXACT) exacerbation per patient		
Least square mean (SE) [†]	92.9 (1.7)	91.3 (1.8)
Percentage of days without symptom-defined (EXACT) or HCRU exacerbation per patient		
Least square mean (SE) [†]	89.3 (1.8)	86.4 (2.0)
Number of HCRU exacerbations in the EXACT subset	147	169
Severity of symptom-defined (EXACT) exacerbations		
n	137	148
Mean (SD)	46.5 (11.2)	44.8 (10.7)
EXACT severity of HCRU exacerbations		
n	143	167
Mean (SD)	44.9 (10.9)	44.7 (9.9)
Mean EXACT total score during HCRU exacerbations		
n	143	167
Mean (SD)	38.2 (9.6)	37.9 (8.8)
Time to first symptom-defined (EXACT) exacerbation, d		
25th percentile (95% CI)	168 (100–275)	118 (86–162)
Median (95% CI)	NE	NE
Analysis of time to first symptom-defined (EXACT) exacerbation		
HR (IND/GLY vs. SFC) (95% CI) [‡]	0.76 (0.56–1.03)	
P value	0.08	
Time to first HCRU exacerbation, d		
25th percentile (95% CI)	159 (85–261)	82 (60–113)
Median (95% CI)	369 (369–NE)	365 (265–NE)
Analysis of time to first HCRU exacerbation		
HR (IND/GLY vs. SFC) (95% CI) [‡]	0.74 (0.56–0.99)	
P value	0.04	

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXACT = Exacerbations of COPD Tool; HCRU = healthcare resource use; HR = hazard ratio; IND/GLY = indacaterol/glycopyrronium; NE = not estimable; SFC = salmeterol/fluticasone propionate.

*Calculated as total number of treatment years [sum of exposure to double-blind drug expressed in years: (days/365.25)/N]. Occurrence rate in 100 patient-years = total number of COPD exacerbation episodes/total number of treatment years × 100. Symptom-defined (EXACT) exacerbations starting between the first dose and 1 d after the date of last treatment are included.

[†]Least square means, including SE for percentage of days without symptom-defined (EXACT) exacerbations, are from a linear mixed model, including terms of treatment, initial baseline, EXACT total score, smoking status at screening, inhaled corticosteroid use at screening, airflow limitation severity, baseline COPD exacerbation history (i.e., number of COPD exacerbations during the past 12 mo prior to study), region, and random effect of center nested within region. For HCRU exacerbations the initial baseline EXACT total score was replaced by the baseline total symptom score.

[‡]HRs, including 95% CI, are from a Cox regression model, including terms of treatment, initial baseline EXACT total score, smoking status at screening, inhaled corticosteroid use at screening, airflow limitation severity, baseline COPD exacerbation history (i.e., number of COPD exacerbations during the past 12 mo prior to study), and region. For HCRU exacerbations, the initial baseline EXACT total score was replaced by the baseline total symptom score.

Figure 1. The effect of indacaterol/glycopyrronium versus salmeterol/fluticasone propionate on the rate and time to first symptom-defined (EXACT) exacerbation in the EXACT subset. CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXACT = Exacerbations of COPD Tool; IND/GLY = indacaterol/glycopyrronium; NS = not significant; SFC = salmeterol/fluticasone propionate.

new instruments that enhance the detection of these unreported events are needed. Several studies have cited the use of the EXACT questionnaire in this regard, with telemonitoring or electronic interfacing systems alerting physicians to the onset of an exacerbation and triggering patient–physician reporting (30–33). In this study, we observed differences between protocol-defined moderate/severe (HCRU) exacerbation rates and symptom-defined exacerbations using the EXACT, with a higher number of HCRU exacerbations than symptom-defined events and a weak

relationship observed between the two types of events. In a study by Mackay and colleagues (34), mean EXACT scores increased significantly by 13% from 42.6 at baseline to 48.0 at exacerbation onset and increased further to a maximum score of 54.1 points. Maximum EXACT scores were significantly higher in treated versus untreated events. Approximately 50% of both diary card–defined and HCRU–defined exacerbations crossed the EXACT event threshold. However, only 27.9% of diary card–defined and 34.6% of HCRU–defined exacerbations fully met the criteria for a

symptom-defined (EXACT) event. Jones and colleagues (6) also found modest concordance between HCRU–defined and symptom-defined (EXACT) events: approximately two-thirds of patients with symptom-defined exacerbation did not have a moderate/severe event, whereas approximately half of the patients experiencing the latter did not have a symptom-defined exacerbation. Our finding of a modest concordance between HCRU and symptom-defined (EXACT) exacerbations is consistent with these studies and should not be misinterpreted

Table 3. Analysis of the Annualized Rate of Symptom-defined (EXACT) Exacerbations: IND/GLY versus SFC

Treatment	n*	Annualized Rate [†] (95% CI)	Comparison	Rate Ratio [‡] (95% CI)	P Value
HCRU events in the EXACT subset					
IND/GLY (n = 233)	231	0.68 (0.50–0.91)	IND/GLY / SFC	0.78 (0.58–1.05)	0.11
SFC (n = 220)	220	0.86 (0.63–1.17)			
All symptom-defined (EXACT) events [§] (whether reported or unreported)					
IND/GLY (n = 233)	231	0.85 (0.63–1.14)	IND/GLY / SFC	0.83 (0.60–1.14)	0.24
SFC (n = 220)	220	1.03 (0.75–1.40)			
Unreported symptom-defined (EXACT) events					
IND/GLY (n = 233)	231	0.68 (0.49–0.94)	IND/GLY / SFC	0.81 (0.57–1.16)	0.25
SFC (n = 220)	220	0.84 (0.60–1.17)			

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXACT = Exacerbations of COPD Tool; HCRU = healthcare resource use; IND/GLY = indacaterol/glycopyrronium; SFC = salmeterol/fluticasone propionate.

*Number of patients included in the analysis.

[†]Derived from a generalized linear model assuming a negative binomial distribution with fixed effects of treatment, initial baseline EXACT total score, baseline COPD exacerbation history (i.e., number of COPD exacerbations during the past 12 mo prior to study), smoking status at screening, inhaled corticosteroid use at screening, airflow limitation severity, and region. As the offset variable, log(exposure time in years) was used.

[‡]A ratio of rates <1 favors the treatment group in the numerator of the ratio.

[§]Symptom-defined (EXACT) exacerbations starting between the first dose and 1 day after the date of last treatment are included.

Figure 2. (A and B) Series plots of mean EXACT total scores of (A) first reported (open squares) and unreported (open circles) symptom-defined (EXACT) exacerbations and of (B) first healthcare resource use exacerbations (solid squares). In A, the analysis is based on patients with at least one symptom-defined (EXACT) chronic obstructive pulmonary disease (COPD) exacerbation. Symptom-defined (EXACT) COPD exacerbations starting between first dose and 1 day after the date of last treatment are included. A symptom-defined (EXACT) COPD exacerbation is considered reported when at least 1 day of the event is in between the time window of start date $\pm$ 7 days of a moderate or severe COPD exacerbation as reported on the electronic case report form. In B, the analysis is based on patients with at least one moderate or severe COPD exacerbation (with a non-missing EXACT total score) between first dose and 1 day after the date of last treatment. COPD exacerbations that occurred within 7 days of each other are collapsed as one event. EXACT = Exacerbations of COPD Tool; HCRU = healthcare resource use.

as a criticism of the EXACT instrument. The EXACT detects events that meet a prespecified symptomatic threshold and are therefore a standardized metric that can be applied across study populations. In contrast, HCRU exacerbations are complex events of variable symptom intensity that typically require the patient to report to a clinic for evaluation and for the clinician to diagnose an exacerbation. Thus HCRU events and symptom-defined (EXACT) events are important but distinct entities to be recognized and counted as separate and complementary endpoints (6, 35). Further work is needed to fully understand the relationship between symptom-defined events (such as those measured using the EXACT) and HCRU exacerbations. The observation of a higher number of HCRU exacerbations than symptom-defined (EXACT) events warrants further study, as this has not been observed in prior studies using the EXACT (6, 35). It is possible that the use of the e-diary within the FLAME study may have prompted early detection of symptom worsening and early treatment. Early treatment has been shown to improve clinical outcomes (17), and therefore it is possible that by ensuring optimal treatment, use of the e-diary could have reduced the likelihood of enough symptom deterioration to trigger a conservative symptom-defined (EXACT) event and therefore have suppressed the observed symptom-defined event numbers. Importantly, however, note that any symptom deterioration captured with the e-diary alerted only the patients, and upon patient reporting, investigators had to confirm and decide whether antibiotic and/or systemic corticosteroid treatment was required for the event, ensuring that overtreatment did not occur.

Table 4. Analysis of the Likelihood of Future Moderate/Severe (HCRU) Exacerbation Risk on the Basis of Previous Symptom-defined (EXACT) Events (EXACT Subset)

No. of Exacerbations between Days 1 and 84	n*	Annualized Rate† (95% CI)	Comparison	Rate Ratio (95% CI)	P Value
Symptom-defined (EXACT) events (EXACT subset)					
0	349	0.49 (0.35–0.68)	0 vs. $\geq$ 1	0.71 (0.47–1.09)	0.12
$\geq$ 1	62	0.69 (0.44–1.09)			

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; EXACT = Exacerbations of COPD Tool; HCRU = healthcare resource use; ICS = inhaled corticosteroid.
*Number of patients included in the analysis.
†Generalized linear model assuming a negative binomial distribution with baseline total symptom score, exacerbation history, smoking status, ICS use, airflow limitation severity, region, and number of exacerbation events (0 or $\geq$ 1) between Days 1 and 84 as fixed effects.

Alongside the small sample size of the EXACT subset, which is a clear limitation of this analysis, another limitation was that validated translations of the EXACT questionnaire were only available in certain countries participating in the FLAME trial, which could have introduced a selection bias. Furthermore, as the questionnaire was optional, it was not evaluated in all patients where it was available, which in itself presents a degree of selection bias. We also acknowledge that overall the EXACT subgroup was younger, had a greater proportion of female participants, a longer duration of COPD, a higher proportion of current smokers, and greater FEV₁ and CAT scores than for patients not included in the EXACT subset, and thus findings may not be generalizable to a wider population. However, high compliance

rates in the use of the EXACT tool (>90% in each treatment arm) were observed during the study, which suggest that the data collected are of robust quality and therefore illustrative of the abilities of the EXACT tool to perform suitably in the population studied. High compliance in the use of the tool has also been reported in other studies (36).

Conclusions

Regardless of the exacerbation definition used (symptom defined using the EXACT or HCRU), IND/GLY was more effective than SFC in reducing and delaying exacerbations in patients with moderate to very severe COPD. In this exploratory analysis of the EXACT subset, trends in favor of IND/GLY versus SFC were observed for both the reduction of, and the time to, first symptom-

defined (EXACT) exacerbation. The low concordance between symptom-defined and moderate/severe (HCRU) exacerbations is consistent with data from other published papers. The results obtained from the EXACT subset were consistent with the overall FLAME study results and support the use of a LABA/LAMA, such as IND/GLY, as the preferred treatment option for patients at risk of exacerbations. ■

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