Supplementary materials

LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD

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METHODS (ADDITONAL DETAILS)

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Study design and treatments

Patients who participated in this study were aged ≥40 years with moderate-to-severe COPD, stage II and III as defined in the GOLD 2010 criteria (1), for example, post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥30%, <80% of the predicted normal value and post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7, and a smoking history of at least 10 pack-years. More information on the inclusion and exclusion criteria is presented in Table S1.

A double-dummy design was used as the identity of the study drugs could not be disguised because of the differences in delivery devices. Patients received medication kits consisting of either active QVA149 with Breezhaler device and placebo SFC with Accuhaler device or placebo QVA149 with Breezhaler device and active SFC with Accuhaler device. Patients were required to take both in the morning and only the Accuhaler device in the evening

Randomization and blinding

All eligible patients were randomized via the interactive response technology (IRT) to receive one of the two treatment arms with a specific unique medication number for the study drug that was to be dispensed into the patient. The randomization number was not disclosed to the investigator using the IRT. The randomization was stratified by smoking status (current/ex-smoker status) and prior ICS use. The randomization

scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Blinding of patients from the investigator staff, people performing the assessments, and data analysts was maintained by ensuring that the randomization data were kept strictly confidential until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, scheduling of administration, appearance, taste, and odor. A double-dummy design was used because the identity of the study drugs could not be disguised due to their different forms. Unblinding was only permitted in the case of patient emergencies and at the conclusion of the study.

Spirometry

FEV_1 and FVC were assessed at Day 1 and at Weeks 6, 12, 18, and 26. FEV_1 and FVC were recorded at all clinic visits, using centralized spirometry, at the following time points relative to the morning dose: 45 and 15 minutes pre-dose; 5 and 30 minutes; 1, 2, 4 hours post-dose on Day 1; and Weeks 12 and 26 in all patients. In a subset of patients (n=81), further spirometry was conducted at 8 and 12 hours post-dose on Day 1 and at Weeks 12 and 26.

Post-dose trough FEV_1 was defined as the mean of FEV_1 values obtained 23 hours 15 minutes and 23 hours 45 minutes post-dose. Peak FEV_1 and FVC were defined as the maximum FEV_1 or FVC over the period from 5 minutes to 4 hours post-dose. Trough FVC was defined as the mean FVC obtained 23 hours 15 minutes and 23 hours 45 minutes post-dose.

Exacerbation definition

Exacerbations were defined as worsening of symptoms that were captured via the e-diary. Moderate and severe exacerbations were also captured in the case report form (CRF). Quality control and reconciliation of the exacerbation data contained within the e-diary and CRF was carried out. The Anthonisen criteria were used to define the symptoms of an exacerbation (2, 3). A COPD exacerbation was considered moderate, if patients were treated with systemic corticosteroids or antibiotics or both, and were considered severe, if patients were hospitalized or experienced an emergency room (ER) visit longer than 24 hours.

Safety analysis

Safety was assessed by monitoring the adverse events (AEs) and serious AEs during the study. Vital signs (electrocardiogram [ECG], pulse rate, and systolic and diastolic blood pressure) and laboratory analyses (hematology, clinical chemistry, and urinalysis) were evaluated as part of the safety assessment.

Statistical methods

Statistical analyses

Efficacy analyses was conducted on the per-protocol set (PPS), which included all patients in the full analysis set population without any major protocol deviations. Major protocol deviations were defined prior to database lock. The PPS was used for the primary analysis and the supportive analysis to assess robustness of the key secondary analysis.

All (mild, moderate, severe) COPD exacerbation was also analyzed using similar statistical models as that used for moderate/severe exacerbations. The negative binomial model and Cox proportional hazard model included treatment, baseline ICS use (Yes/No), baseline total symptom score, baseline COPD exacerbation history (the number of COPD exacerbations in the year prior to screening), FEV_1 reversibility components, smoking history (current/ex-smoker), and region.

Post-hoc analyses were conducted to assess severe COPD exacerbations (with hospitalizations). Due to the smaller number of exacerbations, the analyses for severe COPD exacerbation only included treatment, baseline total symptom score, the number of COPD exacerbations in the year prior to screening, and FEV_1 reversibility components in the model.

Post hoc analyses were performed on the subgroups of patients with and without a baseline history of exacerbation to compare the percentage of patients who experienced an exacerbation while on QVA149 treatment compared with SFC treatment using a Chi-square test (or Fisher's exact test when the expected values in any of the cells of a contingency table are below 5). In addition, the rate of all COPD exacerbations was analyzed in these subgroups of patients with the same negative binomial model used for the full population, except without the baseline COPD exacerbation history term in the model.

The safety set comprised all patients who received one dose of the study drug, and patients were analyzed according to the treatment they received.

RESULTS (ADDITIONAL DETAILS)

Spirometry

Analysis of the change in trough FEV_1 from baseline to Week 26 demonstrated that a higher percentage of patients in the QVA149 group achieved an improvement of ≥100 mL (QVA149 60.6%; SFC 44.2%) or ≥200 mL (QVA149 43.7%; SFC 24.7%) compared with SFC (Table S3). Trough FEV_1 at Week 26 was also analyzed for the subgroups of patients with a smoking history, ICS use at baseline, a severity of COPD, and a COPD exacerbation history. All comparisons favored QVA149 treatment over SFC (Figure S1).

Exacerbations

The total number of all exacerbations (mild, moderate and severe) was lower in the QVA149 treatment arm (105) compared with the SFC treatment arm (131). Furthermore, the rate of all COPD exacerbations per year was lower in the QVA149 (0.59) treatment group when compared with SFC (0.75) treatment arm although this difference did not reach statistical significance (Table S5).

The post-hoc analysis on the annualized rate of severe exacerbations showed a 69% reduction in the QVA149 treatment arm when compared with SFC (*P*=0.023; Table S5). Similarly, the analysis on time to the first severe exacerbation (Figure S2B) showed that QVA149 reduced the hazard of having a severe exacerbation/hospitalization by 68% (*P*=0.027) compared to SFC.

Due to the observed different percentages of patients with a history of exacerbation at baseline in treatment groups (16.4% of QVA149 and 25.2% of SFC), post-hoc analyses were performed on subgroup of patients with or without a baseline history of

exacerbation. In patients with a history of COPD exacerbation, the percentage of patients who experienced a subsequent exacerbation was consistently reduced in the QVA149 treatment arm compared with SFC for all (mild, moderate and severe) exacerbations (QVA149: 24.6%; SFC: 46.2%, P=0.007), moderate or severe exacerbations (QVA149: 19.7%; SFC: 34.4%, P=0.048) and severe (QVA149: 0%; SFC: 7.5%, P=0.043) exacerbations (Figure S3A). Furthermore, the annualized rate of COPD exacerbations was significantly lower in patients with a history of moderate or severe COPD exacerbations at baseline treated with QVA149 compared with SFC group for all exacerbations (rate ratio: 0.43; P=0.003; Table S6), and moderate or severe exacerbations (rate ratio of 0.43;*P*=0.003; Table S6).

In patients without a history of exacerbations at baseline, the percentages of patients who experienced a moderate or severe and severe exacerbations in the QVA149 treatment arm were numerically lower compared to the SFC treatment arm; however the differences were not statistically significant (Figure S3B).

References for online supplement

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2010. Available from: http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf.
2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Annals of internal medicine* 1987; 106: 196-204.
3. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 1998; 157: 1418-1422.

Table S1. Inclusion and exclusion criteria—the LANTERN study

Inclusion criteria

- Male or female adults aged ≥40 years, who have signed an informed consent form prior to initiation of any study-related procedure.
- Patients with moderate-to-severe stable COPD (Stage II or Stage III) according to GOLD guideline (GOLD 2010).
- Current or ex-smokers who have a smoking history of at least 10 pack-years (10 pack-years are defined as 20 cigarettes a day for 10 years or 10 cigarettes a day for 20 years, etc.). An ex-smoker may be defined as a subject who has not smoked for ≥6 months at screening.
- Patients with a post-bronchodilator FEV_1 ≥30% and <80% of the predicted normal and post-bronchodilator FEV_1/FVC <0.7 at Visit 2 (Day –14). Post-bronchodilator refers to 1 hour after sequential inhalation of 80 µg ipratropium bromide (or equivalent dose) and 400 µg salbutamol/albuterol (or equivalent dose).
- Protocol defined mMRC grade of at least 2 at Visit 2.

Exclusion criteria:

General exclusion

- Pregnant or nursing (lactating) women, in whom pregnancy is confirmed by a positive hCG laboratory test.
- Women of childbearing potential.
- Patients with conditions contraindicated for treatment with or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - Anti-cholinergics
    - Long- and short-acting β2-agonists
    - Sympathomimetic amines
    - Lactose or any of the other excipients of the study medication
- Patents with narrow-angle glaucoma, symptomatic BPH or unstable during treatment for BPH, bladder-neck obstruction, moderate-to-severe renal impairment, or urinary retention.
- Patients with a history of long QT syndrome or whose QTc measured at the run-in period (Visit 2; Fridericia's method) is prolonged (>450 ms for males and females), as confirmed by the central ECG assessor.
- Patients who have a clinically significant abnormality on the ECG at the run-in period (Visit 2), who in the judgment of the investigator would be at potential risk if enrolled into the trial (these patients were not re-screened).

- Patients with Type I or uncontrolled Type II diabetes.
- Patients who have not achieved spirometry result at Visit 2 in accordance with the American Thoracic Society/European Respiratory Society (ERS) criteria for acceptability and repeatability.
- Patients with a history of malignancy of any organ system treated or untreated, within the past 5 years whether there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
- Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities that could interfere with the assessment of the efficacy and safety of the study treatment.
- Patients unable to use an electronic patient diary.
- Patients with a body mass index of >40 kg/m^2.

COPD specific exclusion

- Patients requiring long-term oxygen therapy (>12 hours a day) on a daily basis for chronic hypoxemia.
- Patients who have had two or more COPD exacerbations for which they have been treated with antibiotics, systemic steroids (oral or intravenous), or hospitalization in the past year prior to screening (Visit 1).
- Patients who have had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous), or hospitalization in the 6 weeks prior to screening (Visit 1 or between Visit 1 and Visit 3).
- Patients who develop a COPD exacerbation between the screening and the randomization visit (Visits 1 and 3) but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of COPD exacerbation.
- Patients who experience FEV_1 decrease ≥20% between the run-in period and randomization visit (Visits 2 and 3).
- Patients who have had a respiratory tract infection within 4 weeks prior to screening (Visit 1).
- Patients who develop a respiratory tract infection between screening and randomization (up to Visit 3) will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
- Patients with concomitant pulmonary disease (e.g., lung fibrosis, primary bronchiectasis, sarcoidosis, interstitial lung disorder, pulmonary hypertension).
- Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active.
- Patients with pulmonary lobectomy, lung volume reduction surgery, or lung transplantation.

- Patients with (a) any history of asthma or (b) onset of respiratory symptoms prior to the age 40 years.
- Patients with a blood eosinophil count of >600/mm^3 at the run-in period (Visit 2).
- Patients with allergic rhinitis who use an H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose is permitted).
- Patients with a history and diagnosis of α-1 antitrypsin deficiency.
- Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial (maintenance program is permitted).

BPH, benign prostatic hyperplasia; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table S2. Medication allowed in the LANTERN study

	Condition under which medication is permitted
Selective serotonin reuptake inhibitors	Stable dose for at least 1 month prior to Visit 1 and during the study
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Visit 1
H1-antagonists	Stable dose for at least 5 days prior to Visit 1
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to a study visit

Table S3. Analysis of responders of post-dose trough FEV_1 after 26 weeks of treatment

Treatment	n/N' (%)	Comparison	Odds ratio (95% CI)
Patients with a clinical improvement of trough FEV_1 ≥100 mL			
QVA149 (N=372)	215/336 (60.6)	QVA149/SFC	1.88 (1.38, 2.56)***
SFC (N=369)	152/344 (44.2)		
Patients with a clinical improvement of trough FEV_1 ≥200 mL			
QVA149 (N=372)	155/355 (43.7)	QVA149/SFC	2.38 (1.70, 3.33)***
SFC (N=369)	85/344 (24.7)		

****P*<0.001.

Odds ratio, 95% CI, and *P*-value are from a logistic regression model: Logit (proportion)=treatment+baseline FEV1+baseline ICS+FEV_1 reversibility components+smoking status+COPD exacerbation history+region+center (region). Center is included as a random effect nested within region.
CI, confidence interval; n, number of patients who achieved a clinically important improvement of change from baseline on trough FEV_1; N', number of patients with a trough FEV_1 value at both baseline and post-baseline (included in the analysis).

Table S4. Percentage of nights with "no night time awakenings," percentage of days with "no daytime symptoms," and percentage of "days able to perform usual daily activities" over 26 weeks (FAS)

					Treatment difference QVA149/ (SFC)		
Variable	**Treatment**	**n**	**Baseline mean (SE)**	**Treatment LS mean (SE)**	**LS mean (SE)**	**95% CI**	***P*-value**
Percentage of nights with "no night time awakenings"	QVA149 (N=372)	336	55.25 (2.188)	67.57 (2.138)	–0.29 (2.034)	(–4.29, 3.70)	0.886
	SFC (N=369)	322	55.30 (2.267)	67.86 (2.101)			
Percentage of days with "'no daytime symptoms"	QVA149 (N=372)	341	5.78 (1.051)	7.31 (1.466)	–2.90 (1.495)	(–5.84, 0.03)	0.053
	SFC (N=369)	334	3.24 (0.739)	10.22 (1.425)			
Percentage of "days able to perform usual daily activities"	QVA149 (N=372)	341	35.77 (2.074)	44.02 (2.200)	1.85 (2.201)	(–2.47, 6.17)	0.401
	SFC (N=369)	334	33.46 (2.101)	42.16 (2.140)			
Change from baseline in total symptom score	QVA149 (N=372)	353	5.79 (0.145)	–1.06 (0.126)	0.21 (0.119)	(–0.03, 0.44)	0.082
	SFC (N=369)	339	5.97 (0.143)	–1.26 (0.124)			

CI, confidence interval; ICS, inhaled corticosteroid; LS mean, least squares mean; SE, standard error of the mean.

LS mean, 95% CI, and *P*-value are from a MIXED model: percentage of days=treatment+baseline percentage of days+baseline ICS use (yes/no)+FEV_1 reversibility components+baseline smoking status+region+center (region). Center was included as a random effect nested within region.

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Baseline % of days was defined as the % of days in the run-in period.

Table S5. Summary and analysis of COPD exacerbations over 26 weeks by treatment group (full analysis set)

	All COPD exacerbations (mild, moderate and severe)		Severe COPD exacerbations[a]	
	QVA149 (n=372)	SFC (n=369)	QVA149 (n=372)	SFC (n=369)
Number of exacerbations per patient (n [%])				
0	297 (79.8)	272 (73.7)	366 (98.4)	353 (95.7)
1	53 (14.2)	73 (19.8)	6 (1.6)	15 (4.1)
2	17 (4.6)	18 (4.9)	0	1 (0.3)
3	3 (0.8)	3 (0.8)	0	0
≥4	2 (0.5)	3 (0.8)	0	0
Total number of exacerbations	105	131	6	17
Total number of treatment years	179.2	174.9	179.2	174.9
Rate of exacerbations per year	0.59	0.75	0.03	0.09
Treatment comparison vs. SFC				
Ratio of rate (95 % CI)	0.79 (0.58, 1.07)		0.31 (0.11, 0.85)*	

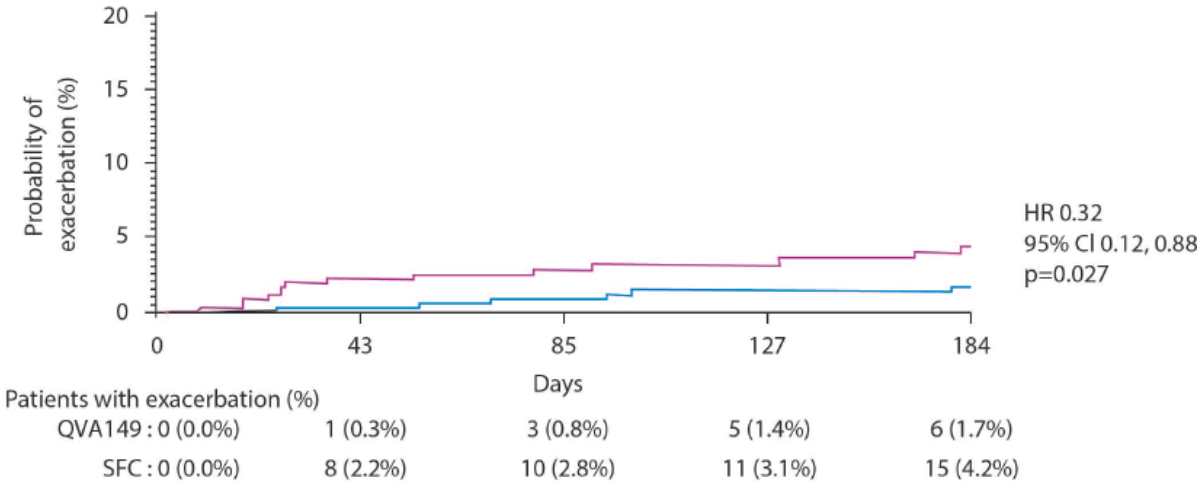
*P<0.05.
[a]Severe exacerbation is defined as an exacerbation that resulted in hospitalization.
CI, confidence intervals; COPD, chronic obstructive pulmonary disease; SFC, salmeterol/ fluticasone

Table S6. Annualized rate of all COPD exacerbation by baseline COPD exacerbation history

Treatment	Annualized rate (95% CI)	Comparison	Rate ratio	95% CI	*P*-value
With COPD exacerbation history					
QVA149 (n=61)	0.78 (0.47, 1.31)	QVA149/SFC	0.43	(0.25, 0.76)	0.003
SFC (n=93)	1.81 (1.31, 2.52)				
Without COPD exacerbation history					
QVA149 (n=311)	0.66 (0.49, 0.87)	QVA149/SFC	0.98	(0.67, 1.43)	0.916
SFC (n=276)	0.67 (0.49, 0.92)				

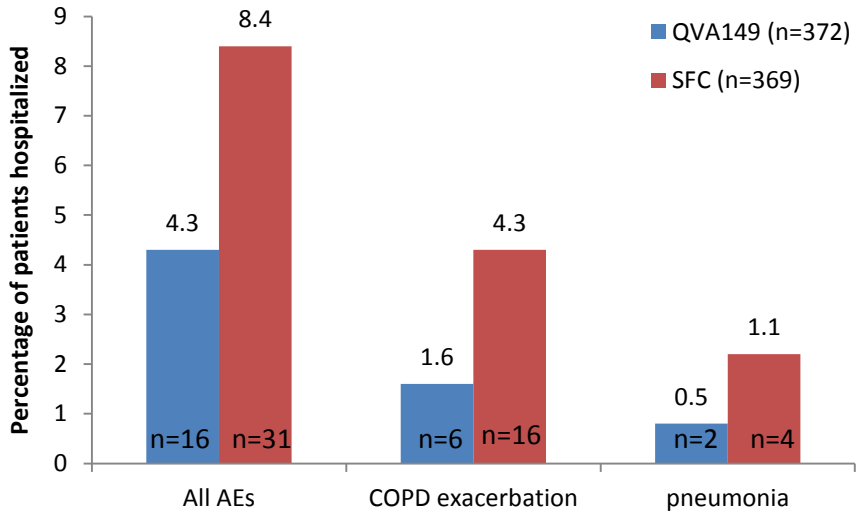
Rate ratio, its 95% CI, and *P*-value are from a negative binomial regression model: log (exacerbation rate)=treatment+smoking status+baseline ICS use (yes/no)+baseline total symptom score+FEV_1 reversibility components+region. Log (length of time in the study) is included in the model as an offset term.
CI, confidence interval.

Figure S1. Kaplan-Meier plots of the time to first severe COPD exacerbation over 26 weeks of treatment (full analysis set)



Abbreviations: CI, confidence intervals; HR, hazard ratio; SFC, salmeterol/fluticasone.

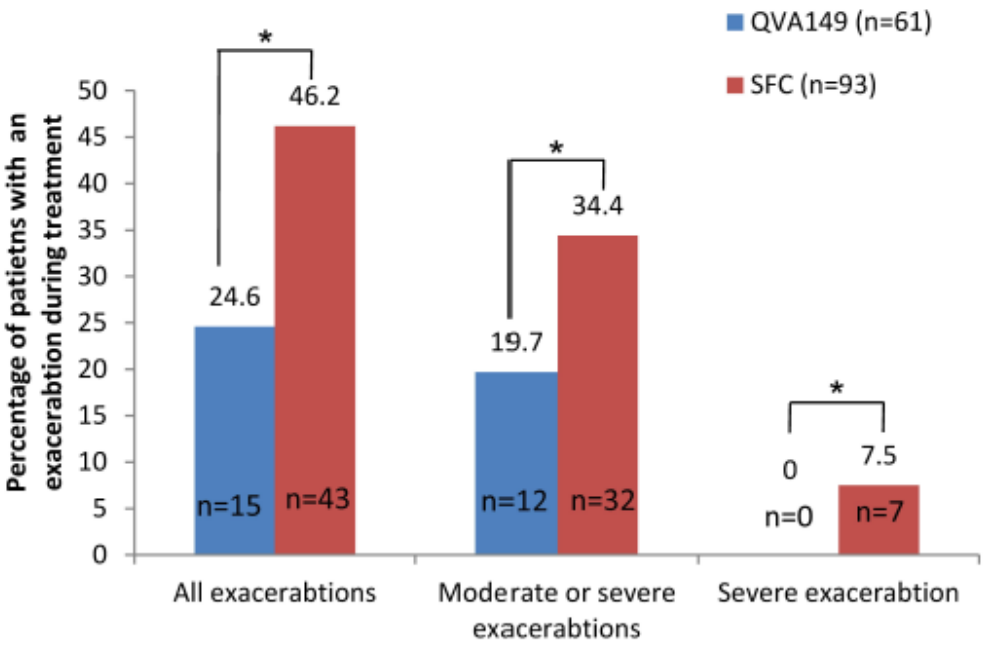
Figure S2. Percentage of patients who experienced hospitalization during the 26 weeks of the LANTERN study. Hospitalization was viewed by all AEs that led to such action or by the two highest causes which were COPD exacerbation and pneumonia



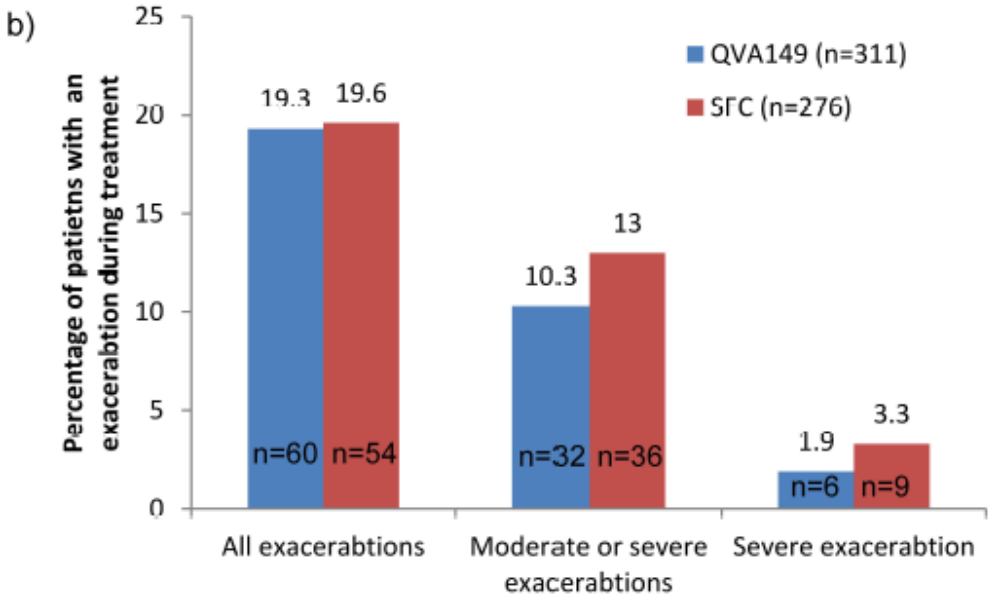
AE, adverse events

Figure S3. Percentage of patients with exacerbations during the LANTERN study in patients with (a) or without (b) a history of exacerbations at baseline

a)



b)



Notes: *P<0.05 from a Chi-square test (or Fisher's exact test, if the expected values in any of the cells of a contingency table are below 5

Abbreviations: SFC, salmeterol/fluticasone