Supplementary Appendix

Efficacy and safety of once-daily QVA149 compared with the free combination of once-daily tiotropium plus twice-daily formoterol in patients with moderate-to-severe COPD (QUANTIFY): a randomised, blinded, non-inferiority study

Roland Buhl[1]*, Christian Gessner[2], Wolfgang Schuermann[3], Karin Foerster[4], Christian Sieder[5], Simone Hiltl[5], Stephanie Korn[6]

1. III. Medizinische Klinik und Poliklinik, Universitätsmedizin der Johannes Gutenberg-Universität Mainz K.d.ö.R., Langenbeckstrasse 1, 55131 Mainz, Germany Tel. +49 6131 17 7270; Fax +49 6131 17 5545; E-mail: roland.buhl@unimedizin-mainz.de
2. Universitätsklinikum Leipzig, Liebigstrasse 18, 04103 Leipzig, Germany and POIS Leipzig GbR, Tauchaer Strasse 12, 04357 Leipzig, Germany
3. Pneumologische Praxis, Bahnhofstrasse 30, 35037 Marburg, Germany
4. Kardio-Pneumologische Praxis, Möllendorffstr. 111, 10367 Berlin, Germany
5. Novartis Pharma GmbH, Roonstrasse 25, Nürnberg, D-90429, Germany
6. Universitätsmedizin der Johannes Gutenberg-Universität, Langenbeckstrasse 1, 55131 Mainz, Germany·

***Corresponding author**

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METHODS

Study design

The study was conducted in 164 centers across Germany, of which 3 were academic centres and the remaining were practising physician offices that included registered pneumologists. The first patient was enrolled on 4 May, 2012, and the last patient completed the study on 2 April, 2013

Inclusion and exclusion criteria

Inclusion criteria

- Male or female adults aged ≥ 40 years, who had signed an informed consent form before initiation of any study-related procedure

- Patients with moderate- to-severe stable chronic obstructive pulmonary disease (COPD; Stage II or Stage III) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2010

- Current or ex-smokers with a smoking history of at least 10 pack-years (10 pack-years was defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.)

- Patients with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥ 30% and < 80% of the predicted normal, and post-bronchodilator FEV_1/FVC < 0·7 at Visit 2 (post referred to 1 hour after sequential inhalation of 84 µg [or equivalent dose] of ipratropium bromide and 400 µg of salbutamol)

Exclusion criteria

- Pregnant women and nursing mothers

- Women of child-bearing potential, unless they met the following definition of post-menopausal criteria: 12 months of natural (spontaneous) amenorrohea, or 6 months of spontaneous amenorrhoea with serum follicle- stimulating hormone (FSH) levels > 40 mIU/mL or 6 weeks after surgical bilateral oophorectomy (with or without hysterectomy)

- Patients 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: anticholinergics, long-/short-acting β_2-agonists, sympathomimetic amines, lactose, or any of the other excipients

- Patients with a history of long QT syndrome or whose corrected QT (QTc) measured at Visit 2 was prolonged (> 450 ms for males and females)

- Patients who had a clinically significant abnormality on the electrocardiogram (ECG) at Visit 2, who in the judgment of the investigator were at potential risk if enrolled into the study (these patients could not be re-screened)

- Patients with paroxysmal (e.g. intermittent) atrial fibrillation. Patients with persistent atrial fibrillation defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months could be considered for inclusion. In such patients, atrial fibrillation had to be present at baseline and screening visits, with a resting ventricular rate of < 100/min

- Patients with Type I or uncontrolled Type II diabetes

- Patients with narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate-to-severe renal impairment or urinary retention (patients with a transurethral resection of prostate [TURP] were excluded from the study. Patients who had undergone full re-section of the prostate, as well as patients who were asymptomatic and stable on pharmacological treatment for the condition were considered for the study)

- Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years, with or without an evidence of local recurrence or metastases, and with the exception of localised basal cell carcinoma of the skin. Patients with non-melanoma skin carcinoma could be considered for the study

- Patients who in the judgement of the investigator had a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to): unstable ischemic heart disease, left ventricular failure (New York Heart Association [NYHA] Class III and IV), history of myocardial infarction, arrhythmia (excluding chronic stable AF). Patients with such events not considered clinically significant by the investigator could be considered for inclusion in the study; uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state; any condition which could compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study

- Patients who were, in the opinion of the investigator, known to be unreliable or non-compliant

- Patients with a body mass index (BMI) of more than 40 kg/m^2

COPD-specific exclusion

- Patients requiring long-term oxygen therapy (>15 h a day) on a daily basis for chronic hypoxemia

- Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalisation in the 6 weeks before pre-screening

- Patients who developed a COPD exacerbation between the pre-screening and randomisation visits (Visits 1 and 3) were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation

- Patients who had a respiratory tract infection within 6 weeks prior to pre-screening (Visit 1). Patients who developed a respiratory tract infection during the screening period (up to Visit 3) were not eligible, but were permitted to be re-screened 6 weeks after the resolution of the respiratory tract infection

- Patients with concomitant pulmonary disease, e.g. pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active) or clinically significant bronchiectasis, lung fibrosis, sarcoidosis, interstitial lung disorder, pulmonary hypertension

- Patients with pulmonary lobectomy, lung volume reduction surgery, or lung transplantation

- Patients with any history of asthma indicated by (but not limited to) a blood eosinophil count of >600/mm^3 (at Visit 2) or onset of symptoms before 40 years

- Patients with eczema (atopic), known for high IgE levels, or a confirmed allergy history within the last 5 years

- Patients with allergic rhinitis using an H_1-antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose was permitted)

- Patients with a history and diagnosis of alpha-1 antitrypsin deficiency

- Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation programme during the study

Concomitant medication allowed in the study

Class of medication	**Condition**
Selective serotonin reuptake inhibitors (SSRIs)	Stable dose for at least 30 days before the screening visit and during the study
Inhaled corticosteroids (stable long-term regimen)	Stable dose for at least 30 days before the screening visit and during the study.
H_1-antagonists	Stable dose for at least 5 days before the

	screening visit (except mizolastine or, terfenadine)
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 h before the study visit

Concomitant medications were received by 52.9% of patients in the QVA149 group, and 50% of patients in the TIO+FOR group. These included medication mentioned in the table above (including COPD-related background therapy with ICS), as well as medication for comorbidities. Therefore, the influence of any of these medications on efficacy or safety results is deemed to be minimal.

Randomisation and blinding

A randomisation list was produced using a validated system that automated the random assignment of treatment arms to randomisation numbers in the specified ratio. The randomisation scheme was reviewed by a Biostatistics Quality Assurance Group, and was locked after approval. Patients were given the lowest available number of the randomisation block assigned to each site, which randomly allocated the patients in a one-to-one ratio to receive either QVA149 or TIO+FOR for a 26-week treatment period. Patients, investigator staff, personnel performing assessments, and data analysts remained blinded from randomisation until database lock. Blinding was achieved by specifying that study medications were dispensed by a third party not involved in other aspects of the study. In addition, a triple-dummy masking was used to blind treatment assignment despite different inhaler devices. Unblinding occurred in the case of emergencies, and at conclusion of the study.

RESULTS

	FAS	**PPS**

	LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])	p value for treatment comparison	LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])	p value for treatment comparison
Symptom score	-1.31 (-3.49 to 0.86)	0.237	–1.09 (–3.53 to 1.35)	0.379
Activity score	–1.03 (–3.07 to 1.02)	0.325	–1.08 (–3.31 to 1.16)	0.344
Impact score	–0.59 (–2.42 to 1.24)	0.528	–0.40 (–2.32 to 1.52)	0.682

CI=confidence interval. FOR=formoterol. FAS=full analysis set. LSM=least squares mean. PPS=per-protocol set. SGRQ-C=St George's Respiratory Questionnaire-COPD. TIO=tiotropium.

Table 1: Sub scores on SGRQ-C (symptom score, activity score and impact score) at Week 26 (FAS and PPS)

Table 2: Subgroup analysis on SGRQ-C (based on gender, age, use of ICS and disease stage) at Week 26 (FAS and PPS)

	FAS			PPS		
	LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])	**p value**	**p (interaction)**	**LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])**	**p value**	**p (interaction)**
Male	–1.12 (–3.20 to 0.95)	0.289		–1.67 (–3.86 to 0.52)	0.135	
Female	0.59 (–2.58 to 3.76)	0.714	0.541	–0·79 (–4·34 to 2·76)	0.662	0.607
Age						
<65	–0.04 (–2.27 to 2.18)	0.969		–0.57 (–2.93 to 1.79)	0.636	
≥65	–1.81 (–4.60 to 0.99)	0.205	0.659	–1.31 (–4.48 to 1.87)	0.418	0.944
ICS use						
No	–1.66 (–3.83 to 0.51)	0.133		–1.41 (–3.65 to 0.82)	0.215	
Yes	0.33 (–2.49 to 3.15)	0.818	0.274	0.35 (–2.81 to 3.52)	0.825	0.373
Disease stage						

at study start (GOLD)						
≤ II	0.05 (–2.34 to 2.43)	0.969		–0.72 (–3.25 to 1.81)	0.575	
≥ III	–1.20 (–3.76 to 1.36)	0.356	0.518	–1.12 (–3.77 to 1.52)	0.404	0.974

CI=confidence interval. FOR=formoterol. FAS=full analysis set. GOLD=Global Initiative for Chronic Obstructive Lung Disease. ICS=inhaled corticosteroid. LSM=least squares mean. PPS=per-protocol set. TIO=tiotropium. p (interaction) is the p value for the interaction term (gender, age class, ICS usage or Gold stage) × treatment

Table 3: Lung function at Week 12 and Week 26 (PPS)

	Week 12		Week 26	
	LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])	**p value for treatment comparison**	**LSM treatment difference QVA149 versus TIO+FOR (LSM [95% CI])**	**p value for treatment comparison**
Pre-dose FEV_1 [L]	0.065 (0.033 to 0.098)	< 0.001	0.073 (0.039 to 0.107)	< 0.001
Post-dose FEV_1 [L]	0.019 (-0.013 to 0.050)	0.248	0.022 (–0.013 to 0.056)	0.216
Pre–dose FVC [L]	0.097 (0.041 to 0.153)	< 0.001	0.082 (0.024 to 0.140)	0.006
Post-dose FVC [L]	0.002 (–0.056 to 0.059)	0.951	0.013 (–0.046 to 0.071)	0.677

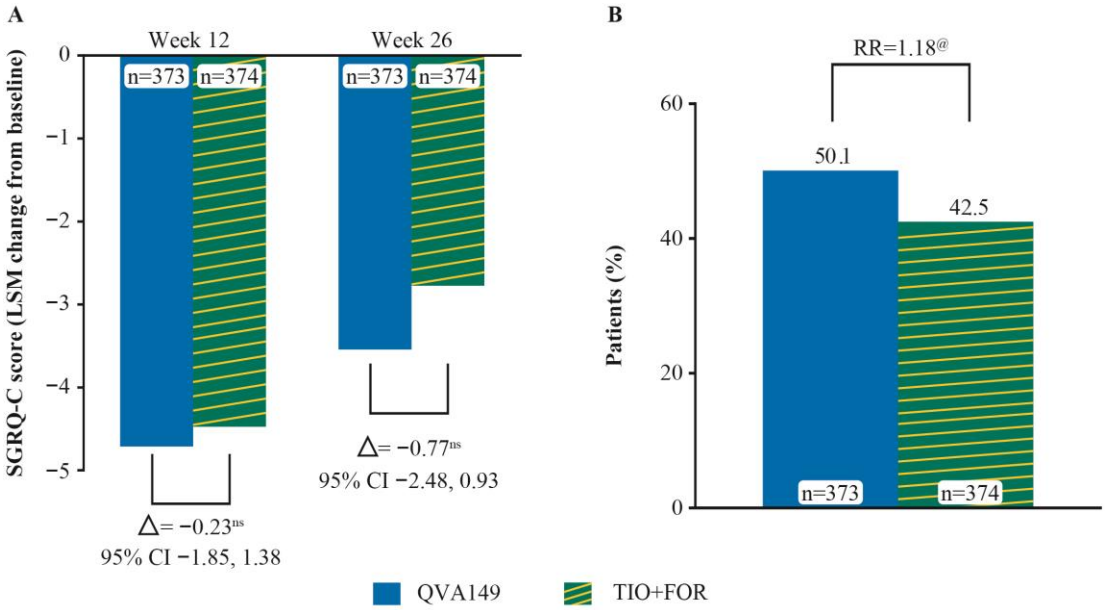
CI=confidence interval. BDI=baseline dyspnoea index. CAT=COPD assessment test. FEV_1=forced expiratory volume in one second. FOR=formoterol. FVC=forced vital capacity. LSM=least squares mean. PPS=per-protocol set. TDI=transition dyspnoea index. TIO=tiotropium.

Table 4: Analysis of rate of moderate or severe COPD exacerbations over the treatment period (FAS)

	QVA149 (110/50 µg)	TIO (18 µg) +FOR (12 µg)	RR (95% CI)	P value
Moderate/severe	62 (13.0)	70 (15.3)	0.85 (0.62, 1.17)	0.323
Moderate	52 (10.9)	61 (13.3)	0.82 (0.58, 1.16)	0.264
Severe	10 (2.1)	11 (2.4)	0.88 (0.38, 2.01)	0.759

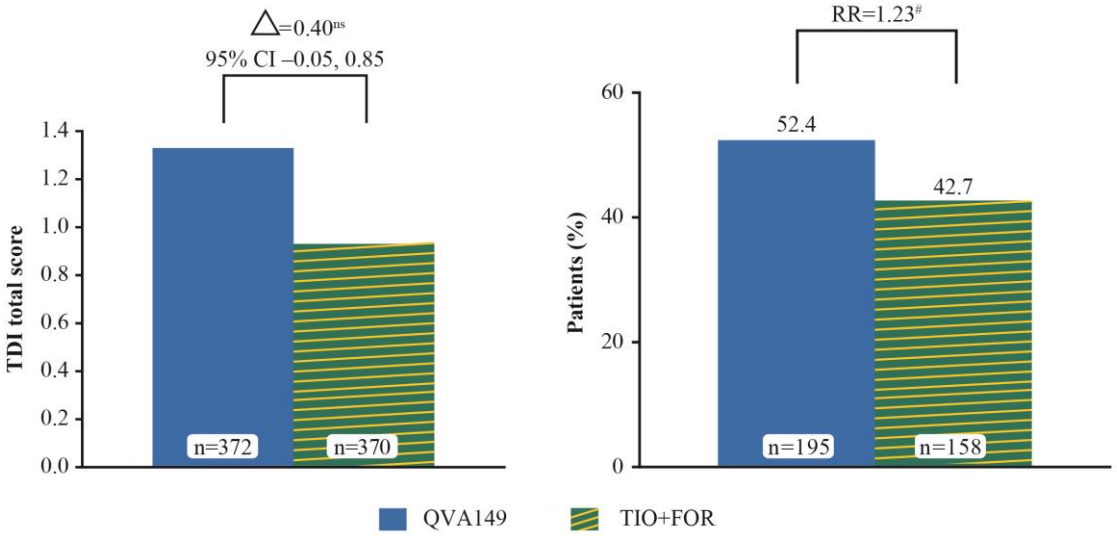
Data are presented as n (%) unless otherwise stated. An exacerbation was defined as the presence of two major symptoms (dyspnoea, sputum volume, sputum purulence) for at least 2 consecutive days or a worsening of one major symptom together with an increase in any one minor symptom (sore throat, colds, fever without other cause, cough, wheeze) for at least 2 consecutive days. CI=confidence interval. FOR=formoterol. FAS=full analysis set. RR=risk ratio. TIO=tiotropium

Figure 1: Per-protocol analysis of SGRQ-C total score after 26 weeks (A) LSM change from baseline in SGRQ-C total scores during treatment and (B) percentages of patients achieving the minimum clinically important difference (≥4 units) in SGRQ-C score after 26 weeks



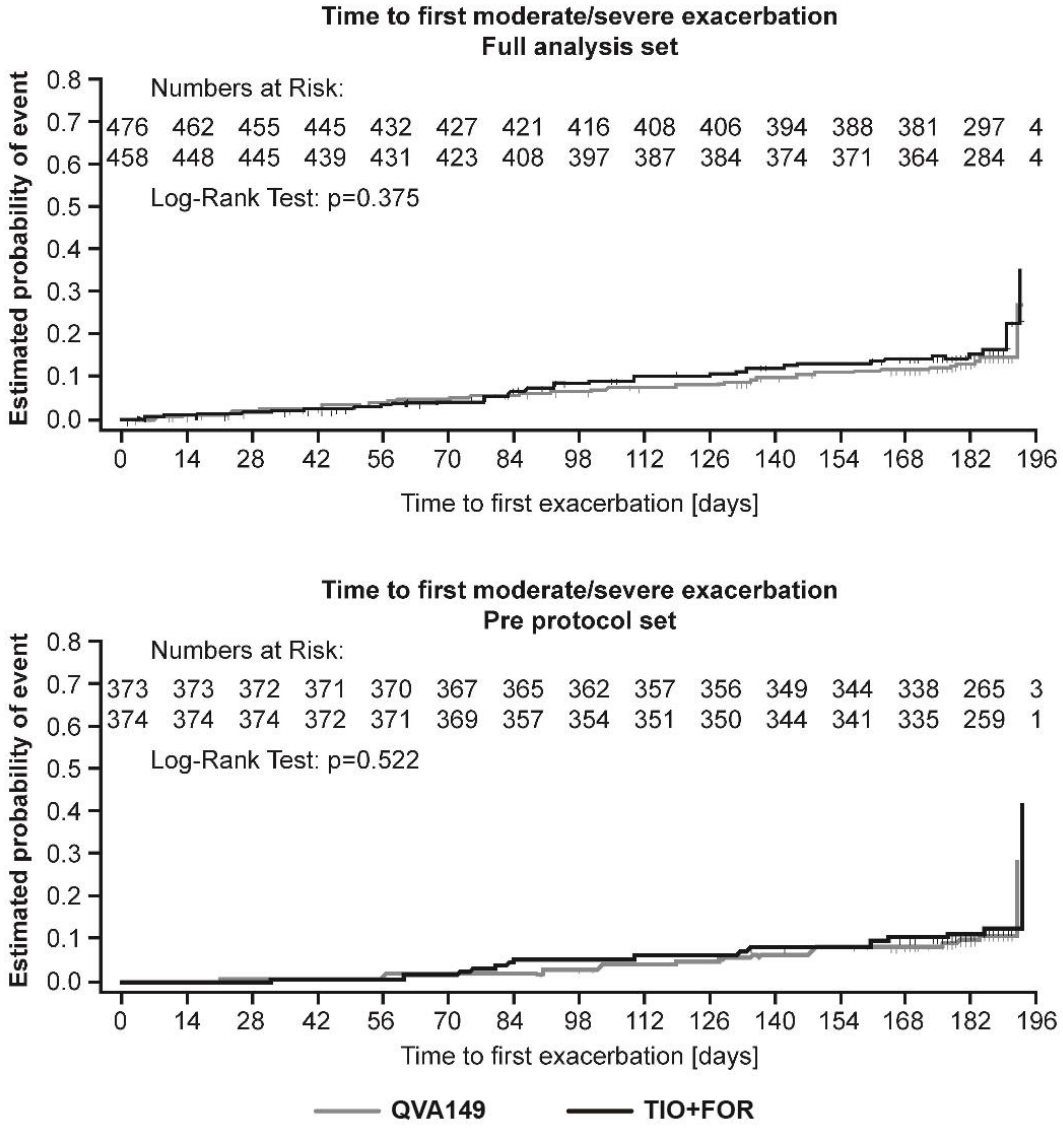
CI=confidence interval. FOR=formoterol. FAS=full analysis set. LSM=least squares mean. PPS=per-protocol set. SGRQ-C=St George's Respiratory Questionnaire-COPD. TIO=tiotropium. ns=not significant. @p<0.05

Figure 2: Per-protocol analysis of TDI total score (A) TDI total score (LSM) after 26 weeks and (B) percentages of patients achieving the minimum clinically important difference (≥1 units)



CI=confidence interval. FOR=formoterol. FAS=full analysis set. LSM=least squares mean. PPS=per-protocol set. TIO=tiotropium. TDI=transition dyspnoea index. ns=not significant. #p<0.01

Figure 3: Time to first moderate or severe COPD exacerbation up to Week 26 (FAS and PPS)



FOR=formoterol. FAS=full analysis set. PPS=per-protocol set. TIO=tiotropium