CLINICAL INVESTIGATION

Dual bronchodilation for the treatment of chronic obstructive pulmonary disease: a review of the latest clinical data

Treating chronic obstructive pulmonary disease with long-acting bronchodilators improves lung function and patient-reported outcomes such as dyspnea, health-related quality of life and exacerbations. Combinations of long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are an alternative treatment recommendation for patients in GOLD Groups B to D and those who remain symptomatic when treated with a single bronchodilator. This review summarizes evidence supporting the efficacy and safety of fixed-dose LABA/LAMAs glycopyrronium/indacaterol (QVA149) and umeclidinium/vilanterol. Considerable clinical trial data are available demonstrating improvements in lung function and patient-reported outcomes with QVA149 and umeclidinium/vilanterol compared with their monocomponents and other comparators. As data supporting the efficacy and safety of LABA/LAMA fixed-dose combinations continue to emerge, dual bronchodilation may feature increasingly in future chronic obstructive pulmonary disease treatment algorithms.

Keywords: COPD • dual bronchodilation • long-acting bronchodilators • lung function • patient-reported outcomes • QVA149 • safety • umeclidinium/vilanterol

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Background

Bronchodilators continue to evolve as the core of therapy in chronic obstructive pulmonary disease (COPD) treatment strategies and guidelines, such as the updated Global initiative for chronic Obstructive Lung Disease (GOLD) strategy document [1]. Long-acting formulations of both classes of bronchodilators – long-acting muscarinic antagonists (LAMA) and long-acting β_2-agonists (LABA) – provide improvements in lung function and the patient-reported outcomes dyspnea and health-related quality of life (HRQoL), as well as a reduction in rescue medication use and the rate of exacerbations [2–4].

In addition to the improvements observed with LABAs and LAMAs when administered as monotherapy, free combinations of LABAs and LAMAs can lead to improvements in lung function measures and dyspnea, and a reduction in rescue medication use compared with the use of a single bronchodilator (Supplementary Table 1). The LAMA component studied in many of these combinations is the once-daily, long-acting bronchodilator tiotropium, administered alongside the LABAs formoterol [5–9], salmeterol [10], olodaterol [11] or indacaterol [12] via separate inhalers. Although combined bronchodilator therapy in free combinations can improve lung function relative to monocomponents, data regarding the additional benefits on patient-reported outcomes have been inconclusive in the past [13]. Therefore, combinations of bronchodilators are currently recommended in the GOLD strategy as an 'alternative' therapy for patients in groups B to D [1]. In particular, the addition of a second bronchodilator is advised for patients who remain symptomatic when treated with one bronchodilator alone [1].

The documented improvements in lung function measures with free combinations of bronchodilators over monotherapies pro-

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vide a rationale for developing bronchodilators in fixed-dose combinations. This rationale is supported by the clinical efficacy of the fixed-dose combination of short-acting bronchodilators albuterol and ipratropium (short-acting β_2-agonist/muscarinic antagonist) compared with either drug alone [14,15]. In addition, the distinct but additive mechanisms of action of β_2-agonists and muscarinic antagonists (Figure 1) support the development of fixed-dose combinations of bronchodilators in a single inhaler. β_2-agonists stimulate smooth muscle relaxation directly through stimulation of adenylyl cyclase, which leads to subsequent increases in cyclic adenosine monophosphate and activation of protein kinase A [16]. In contrast, the presence of muscarinic antagonists indirectly leads to bronchodilation by inhibiting the action of acetylcholine at airway M_3 muscarinic receptors, thereby preventing activation of protein kinase C and increases in intracellular calcium ions, which cause bronchoconstriction [17].

Preclinical observations suggest that targeting two different pathways could produce a greater bronchodilatory effect than targeting a single pathway. Hypotheses on how greater bronchodilation may result from combining LABAs and LAMAs include the varied distribution of β_2-adrenergic receptors [18,19] and M_3 receptors (which could lead to an increased coverage of airways) [18,20]; the temporal variations in sympathetic and parasympathetic activities [21–23]; and interactions between the LABA and LAMA cellular pathways [17,24–26]. Thus administration of long-acting bronchodilators in fixed-dose LABA/LAMA combinations is supported by both scientific rationale and the clinical efficacy of free combinations of LABAs and LAMAs and a fixed-dose short-acting β_2-agonist/muscarinic antagonist combination.

Fixed-dose LABA/LAMAs approved or under investigation for use in the treatment of COPD include glycopyrronium plus indacaterol (QVA149), umeclidinium plus vilanterol, glycopyrrolate plus formoterol, tiotropium plus olodaterol and aclidinium plus formoterol (Table 1). Recently, considerable data from Phase III trials evaluating the efficacy and

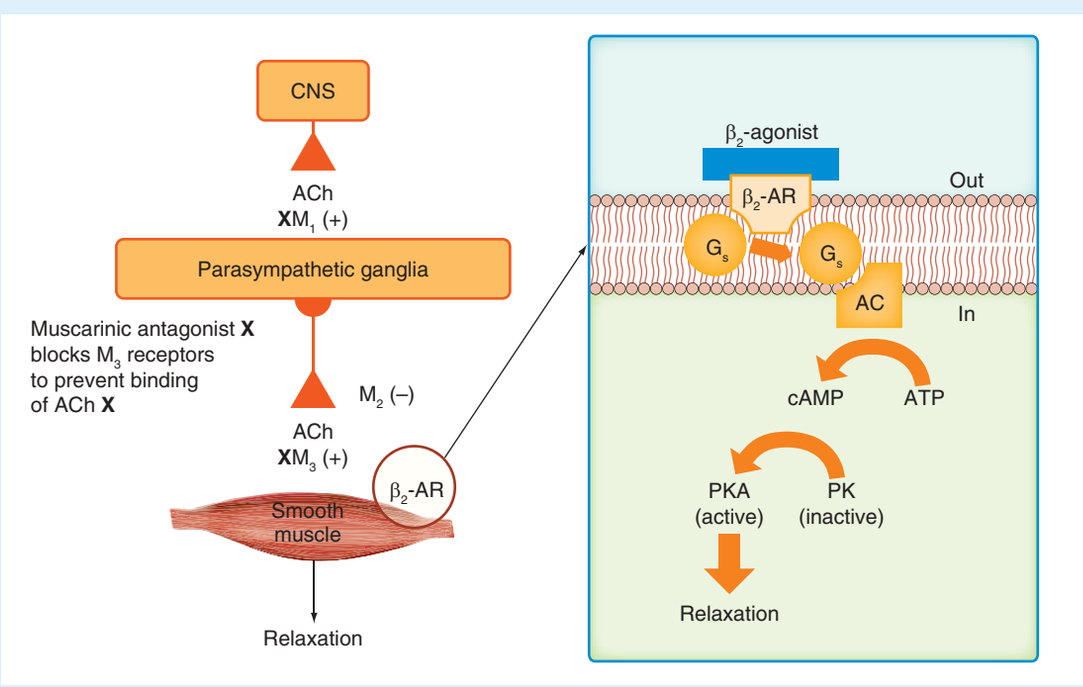

Figure 1. Mechanism of action of muscarinic antagonists and β_2-agonists. Postganglionic, parasympathetic cholinergic nerves release acetylcholine (ACh), a neurotransmitter that regulates muscle tone and bronchoconstriction. ACh binds and activates muscarinic type 1 (M_1) and 3 (M_3) receptors, leading to bronchoconstriction, whereas the binding of ACh to M_2 receptors inhibits ACh release. ACh-binding at M_3 receptors activates protein kinase C and increases intracellular calcium levels, leading to airway smooth muscle contraction [17]. Muscarinic antagonists prevent contraction through inhibiting ACh action at M_3 receptors. β_2-adrenoceptors are activated by β_2-agonists, resulting in increased cAMP levels, which in turn leads to the activation of PKA and subsequent smooth muscle relaxation and bronchodilation [96].
AC: Adenylyl cyclase; ACh: Acetylcholine; ATP: Adenosine triphosphate; β_2-AR: β_2 adrenoceptor; Gs: Stimulatory G-protein; $M_1/M_2/M_3$: Muscarinic receptor types 1/2/3.
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Table 1. Summary of fixed-dose long-acting β_2-agonist/long-acting muscarinic antagonist combinations approved or under investigation for use in chronic obstructive pulmonary disease treatment.

Combination	Dosing	Development stage	Approval status of monocomponents	Manufacturer
Glycopyrronium/ indacaterol	q.d.	Approved (EU, Japan and Canada)	Glycopyrronium✓ Indacaterol✓	Novartis
Umeclidinium/ vilanterol	q.d.	Approved (USA and Canada)	Umeclidinium[†]× Vilanterol[‡]×	Theravance/GSK
Aclidinium/formoterol	b.i.d.	Phase III	Aclidinium✓ Formoterol✓	Almirall/Forest
Glycopyrrolate/ formoterol	b.i.d.	Phase III	Glycopyrrolate× Formoterol✓	Pearl Therapeutics/ AstraZeneca
Tiotropium/olodaterol	q.d.	Phase III	Tiotropium✓ Olodaterol[§]✓	Boehringer Ingelheim

[†]Received a positive opinion from Committee for Medicinal Products for Human Use for use as monotherapy in the EU to relieve symptoms in adults with COPD and is currently under review by the US FDA.
[‡]Vilanterol 25 µg has been approved in a fixed-dose combination with fluticasone furoate as a treatment for COPD in the USA (BREO™ ELLIPTA™) and EU (RELVAR® ELLIPTA®).
[§]Olodaterol 5 µg is approved for use in the treatment of COPD in the UK, Denmark, Iceland, Canada and Russia; approval by health authorities in the USA and other countries worldwide are pending.
b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease; GSK: GlaxoSmithKline; q.d.: Once daily.

safety of QVA149 and umeclidinium/vilanterol have become available. QVA149 110/50 µg, a combination of the LAMA glycopyrronium and LABA indacaterol, is the first once-daily fixed-dose LABA/LAMA combination in a single inhaler to be approved for use in the treatment of COPD [27]. Both components of QVA149 have been approved as monotherapies for maintenance treatment of COPD. Glycopyrronium bromide, a once-daily LAMA, was approved at a dose of 50 µg, and indacaterol was the first once-daily, fast-acting LABA to be approved, at doses of 150 µg and 300 µg. Both glycopyrronium and indacaterol provide improvements in lung function, health status, dyspnea, rescue medication use, exercise endurance time and rate of exacerbations [28–32]. Both monocomponents and the QVA149 combination are administered via the Breezhaler® device. The indacaterol dose in the QVA149 combination is 110 µg; based on *in vitro* performance data, the dose of indacaterol delivered to the lung is expected to be equivalent to the 150 µg dose delivered in the monotherapy [33].

Once-daily umeclidinium/vilanterol (62.5/25 µg), administered using the ELLIPTA™ inhaler, has been approved for the treatment of COPD by the US FDA [34] and has received a positive opinion recommending marketing authorization from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) [35]. Neither monocomponent of umeclidinium/vilanterol is currently approved as monotherapy for the treatment of COPD. However, umeclidinium, an investigational once-daily LAMA, has recently received a positive opinion from the CHMP [36]. Umeclidinium has demonstrated significant improvements in lung function, health status, dyspnea, rescue medication use and exacerbations [37–39]. Vilanterol, a once-daily LABA, has demonstrated statistically significant improvements in lung function, health status, dyspnea and rescue medication use [38,40].

Here, we review the available efficacy and safety data from the QVA149 and umeclidinium/vilanterol Phase III clinical trials and discuss the potential impact of this information on the placement of LABA/LAMA combinations in the COPD treatment algorithm.

Methods

Relevant medical literature on QVA149 and umeclidinium/vilanterol was identified by searching the PubMed (Medline) database for articles published in English since 2009, limited to "randomized controlled trials", "meta-analysis" or "review" articles. Search terms included: "chronic obstructive pulmonary disease" OR "COPD" AND "long-acting β_2-agonist", "long-acting muscarinic agonist", "LABA/LAMA", "dual bronchodilation", "QVA149", "indacaterol/glycopyrronium", "glycopyrronium", "NVA237", "indacaterol", "QAB149", "umeclidinium", "GSK573719", "vilanterol", "GW642444", "umeclidinium/vilanterol", AND "UMEC/VI". We also manually examined bibliographies from publications identified through the initial searches for further relevant literature. Similar searches were applied to congress websites and abstract

books, clinical trials registries/databases and the websites of the US FDA and European Medicines Agency. Studies in patients with COPD who received QVA149 or umeclidinium/vilanterol were selected. We focused on large, well-designed, randomized controlled trials with appropriate statistical methodology to ensure that high-quality evidence was considered.

Clinical development programs

The QVA149 Phase III IGNITE (indacaterol and glycopyrronium bromide clinical studies) clinical trial program consists of 11 studies and involves more than 10,000 patients across 52 countries [27]. Studies in the IGNITE program were designed to evaluate the efficacy and safety of QVA149 compared with its monocomponents and current standards of care in the target population (according to the GOLD recommendations at the time of study initiation). Eight studies in the IGNITE program were completed in 2012 (SHINE, ILLUMINATE, BRIGHT, ENLIGHTEN, SPARK, ARISE, BLAZE and BEACON; Supplementary Table 2). SHINE and ILLUMINATE were 26-week studies, which investigated the efficacy and safety of QVA149 110/50 µg once daily (q.d.) versus indacaterol 150 µg q.d., glycopyrronium 50 µg q.d., open-label tiotropium 18 µg q.d. and placebo (SHINE), and versus salmeterol/fluticasone propionate (SFC) 50/500 µg twice daily (b.i.d.; ILLUMINATE) [41,42]. BRIGHT was a 3-week, three-period crossover study comparing the effect of QVA149 on exercise endurance against placebo and blinded tiotropium 18 µg q.d. [43]. ENLIGHTEN evaluated the long-term safety of QVA149 versus placebo over 52 weeks [44]. SPARK compared the effect of QVA149 on the rate of exacerbations with glycopyrronium 50 µg q.d. and open-label tiotropium 18 µg q.d. over 64 weeks [45]. ARISE was a 52-week study that evaluated the long-term safety of QVA149 versus open-label tiotropium 18 µg q.d. in Japanese patients [46]. BLAZE compared the effect of QVA149 on patient-reported dyspnea with placebo and blinded tiotropium 18 µg q.d. in a three-period crossover study over 6 weeks [47]. BEACON evaluated the efficacy (non-inferiority) and safety of QVA149 compared with the concurrent administration of indacaterol 150 µg q.d. and glycopyrronium 50 µg q.d. in free combination over 4 weeks [48].

The umeclidinium/vilanterol core Phase III program comprises four primary efficacy studies (two placebo-controlled and two active-controlled), two exercise endurance studies and one long-term safety study (Supplementary Table 3). Studies DB2113361 and DB2113373 were 24-week, placebo-controlled studies evaluating the efficacy and safety of umeclidinium/vilanterol compared with placebo and the monocomponents umeclidinium and vilanterol. The studies were replicate in design with the exception of the umeclidinium/vilanterol and umeclidinium dose evaluated: study DB2113361 compared umeclidinium/vilanterol 125/25 µg q.d. with umeclidinium 125 µg q.d. and vilanterol 25 µg q.d. [49], whereas study DB2113373 compared umeclidinium/vilanterol 62.5/25 µg q.d. with umeclidinium 62.5 µg q.d. and vilanterol 25 µg q.d. [38]. Studies DB2113360 and DB2113374 were also 24 weeks in duration and evaluated the efficacy and safety of both doses of umeclidinium/vilanterol (62.5/25 µg and 125/25 µg) compared with tiotropium 18 µg q.d. and either vilanterol 25 µg q.d. [50] or umeclidinium 125 µg q.d. [51]. They were also replicate in design with the exception of the choice of monocomponent comparator. Studies DB2114417 and DB2114418 compared the effect of both doses of umeclidinium/vilanterol on exercise endurance and lung function with umeclidinium (62.5 µg and 125 µg), vilanterol and placebo using an incomplete block crossover design with treatment periods of 12 weeks [52]. Study DB2113359 was a long-term safety study that evaluated the safety and tolerability of umeclidinium/vilanterol 125/25 µg q.d. and umeclidinium 125 µg q.d. compared with placebo over 52 weeks [53].

Two further studies, DB2116133 and ZEP117115, were recently completed. Study DB2116133, completed in May 2013, used a crossover design to evaluate the lung function response to umeclidinium/vilanterol 62.5/25 µg q.d. over 2 weeks in patients who demonstrated a response to either umeclidinium 62.5 µg q.d. or vilanterol 25 µg q.d. to determine whether additional benefit was provided by umeclidinium/vilanterol [54]. Study ZEP117115, completed in September 2013, was a 24-week study that evaluated the efficacy and safety of umeclidinium/vilanterol 62.5/25 µg q.d. compared with tiotropium 18 µg q.d. [55]. Results have not yet been reported.

As the lower dose of umeclidinium/vilanterol (62.5/25 µg) has been approved by the FDA for use in the USA and has received a positive opinion from the CHMP in Europe, we focus on this dose for the presentation of efficacy data.

Baseline demographics

The mean age of patients receiving QVA149 in the IGNITE studies ranged from 62 to 64 years in most of the studies, and all studies enrolled patients with moderate-to-severe COPD, with the exception of SPARK, in which 79% of patients had severe COPD and 21% had very severe COPD [41–48]. In SPARK, patients were required to have experienced at least one moderate or severe exacerbation in the previous year [45]; in contrast, patients enrolled in the ILLUMINATE study

were required to have experienced no moderate or severe exacerbations in the previous year [42]. In studies without specific exacerbation-related eligibility criteria, between 16 and 32% of patients experienced at least one moderate or severe COPD exacerbation in the year prior to study entry [41,43,44,46–48].

The mean age of patients receiving umeclidinium/vilanterol 62.5/25 µg in a pooled dataset of the primary efficacy studies was 64 years, and enrolled patients had moderate-to-very severe COPD (with 11% of patients in the combined umeclidinium/vilanterol 62.5/25 µg arms having very severe disease at baseline) [56,57]. In the year prior to study entry, 27% of patients had at least one COPD exacerbation [56,57].

Lung function

QVA149 improved lung function over an array of measures (Table 2). Significant improvements were observed at 26 weeks in trough forced expiratory volume in 1 s (FEV_1) (Figure 2), peak FEV_1 and FEV_1 area under the curve $(AUC)_{0–12h}$ versus placebo in the SHINE study (least squares mean [LSM] treatment difference 200 ml [95% CI: 170–240], 330 ml [95% CI: 290–360] and 330 ml [95% CI: 250–420], respectively; all $p < 0.001$) [41]. Significant improvements in these measures were also observed with QVA149 versus indacaterol, glycopyrronium and tiotropium in the SHINE study [41]. In the ILLUMINATE study, QVA149 significantly improved predose trough FEV_1, peak FEV_1 and FEV_1 $AUC_{0–12h}$ (Figure 3) versus SFC at week 26 (LSM treatment difference 103 ml [95% CI: 65–141], 155 ml [95% CI: 115–194] and 138 ml [95% CI: 100–176], respectively; all $p < 0.001$) [42]. Predose trough FEV_1 was significantly improved with QVA149 versus glycopyrronium and tiotropium at 64 weeks in the SPARK study [45]. In the BEACON study, QVA149 demonstrated non-inferiority compared with concurrent administration of a free combination of inda-

Table 2. Treatment difference with QVA149 compared with placebo, monocomponents and standards of care, tiotropium and salmeterol/fluticasone propionate.

Study	Comparator arm† (n)	Trough FEV_1, ml (95% CI)‡	Peak FEV_1, ml (95% CI)‡	FEV_1 $AUC_{0–12h}$, ml (95% CI)§	FEV_1 $AUC_{0–4h}$, ml (95% CI)‡
QVA149 110/50 µg q.d. vs placebo					
SHINE	232	200 (170–240)*	330 (290–360)*	330 (250–420)*	340 (300–370)*
BLAZE	218	NR	NR	NR	330 (310–360)*
QVA149 110/50 µg q.d. vs Ind 150 µg q.d.					
SHINE	476	**70 (50–100)***	120 (90–140)*	130 (60–190)*	110 (80–140)*
QVA149 110/50 µg q.d. vs Gly 50 µg q.d.					
SHINE	473	**90 (60–110)***	130 (100–160)*	130 (60–190)*	140 (110–170)*
SPARK	739	70 (50–100)*	NR	NR	NR
QVA149 110/50 µg q.d. vs Ind 150 µg + Gly 50 µg q.d.¶					
BEACON	97	**-5 (-51–40)#**	NR	NR	-12 (-59–34)NS
QVA149 110/50 µg q.d. vs tiotropium 18 µg q.d.††					
SHINE	480	80 (50–100)*	130 (100–160)*	120 (60–190)*	130 (110–160)*
BLAZE	220	NR	NR	NR	110 (80–130)*
SPARK	737	60 (30–80)*	NR	NR	NR
QVA149 110/50 µg q.d. vs SFC 50/500 µg b.i.d.					
ILLUMINATE	264	103 (65–141)*	155 (115–194)*	**138 (100–176)***	NR

Values are mean treatment differences. Bold text indicates primary end points.
*$p < 0.001$.
†QVA149 n = 474 (SHINE); 223 (BLAZE); 729 (SPARK); 84 (BEACON); and 258 (ILLUMINATE).
‡At week 26 in SHINE and ILLUMINATE, at week 6 in BLAZE, at week 64 in SPARK and at week 4 in BEACON.
§At week 26 in the serial spirometry subset (n = 294) in SHINE and full analysis set in ILLUMINATE.
¶Free combination.
#Noninferiority demonstrated.
††Open-label in SHINE and SPARK, blinded in BLAZE.
b.i.d.: Twice daily; FEV_1: Forced expiratory volume in 1 s; Gly: Glycopyrronium; Ind: Indacaterol; NR: Not reported (analysis was not performed or data have not been published); NS: Not statistically significant; q.d.: Once daily; SFC: Salmeterol/fluticasone propionate.
Data taken from [41,42,45,47,48,97,98,99] and [Novartis, Unpublished Data].

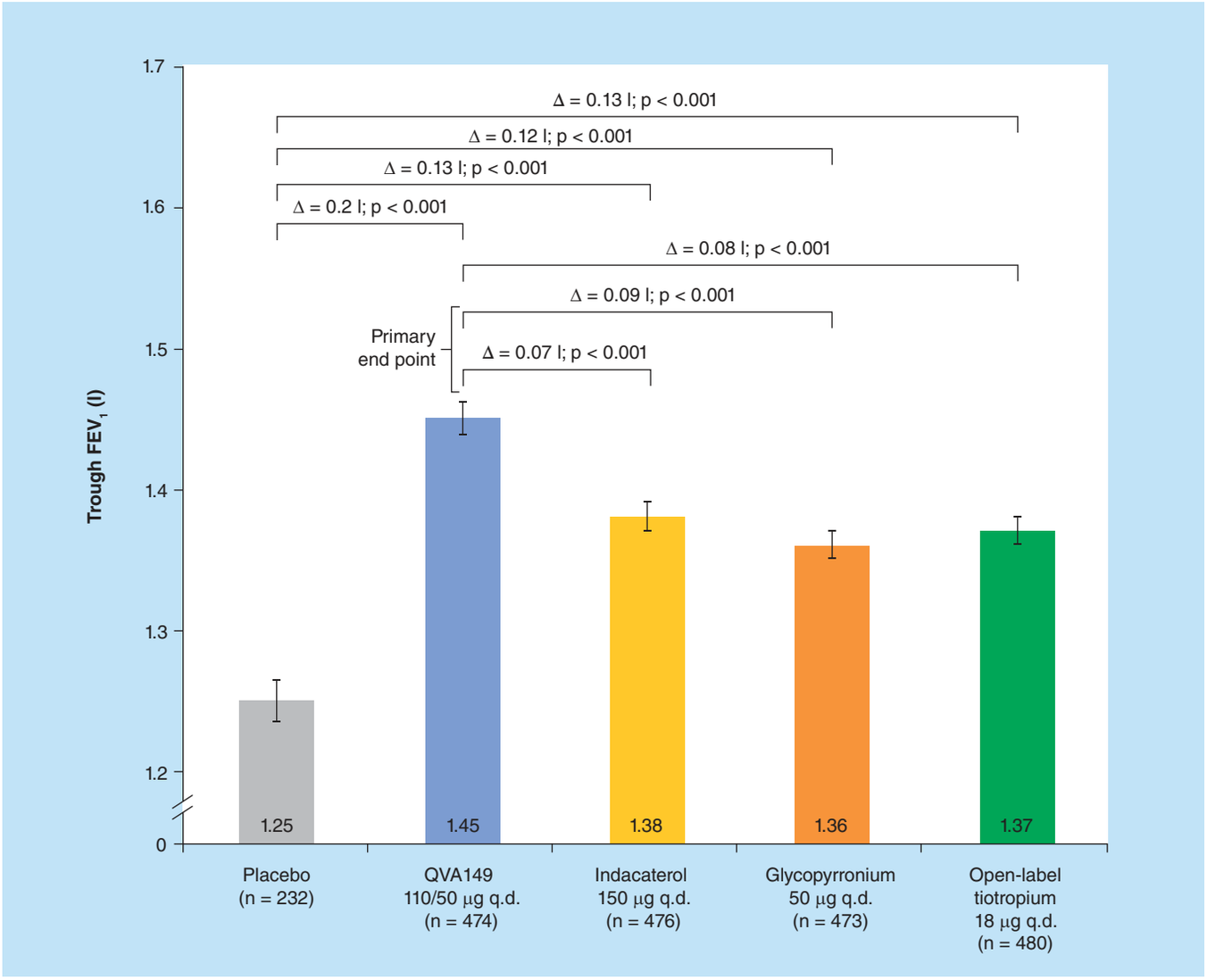

Figure 2. Trough forced expiratory volume in 1 s at week 26 in the SHINE study. Data are least-squares mean ± standard error. One-sided adjusted p-values are presented for comparisons in the statistical gate keeping procedure and two-sided p-values are presented for all other comparisons.
FEV_1: Forced expiratory volume in 1 s; n: Number per treatment group in the full analysis set; q.d.: Once daily.
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caterol 150 µg and glycopyrronium 50 µg on trough FEV_1 at week 4 [48].

In the SHINE study, QVA149 significantly improved trough FEV_1 on day 1 versus placebo, monocomponents and tiotropium, and this improvement was sustained throughout the study ($p < 0.001$ at all timepoints) [41]. In a *post hoc* analysis, a greater proportion of patients achieved an increase in trough FEV_1 at week 26 from baseline >100 ml and >200 ml with QVA149 compared with placebo, the monocomponents and tiotropium (Supplementary Table 4) [41]. In the same study, serial spirometry was conducted in a subpopulation of 294 patients for 12 h at day 1 and for 24 h at week 26 (Figure 4). Statistically significant improvements in FEV_1 were observed compared with placebo ($p < 0.001$) at all assessed timepoints and compared with indacaterol, glycopyrronium and tiotropium at almost all of the assessed timepoints ($p < 0.05$) on day 1 and week 26 [41]. At week 26, QVA149 provided improvements in peak FEV_1 versus placebo, indacaterol, glycopyrronium and tiotropium, with treatment differences of 400 ml (95% CI: 310–490), 170 ml (95% CI: 100–240), 150 ml (95% CI: 80–220) and 160 ml (95% CI: 90–230), respectively (all $p < 0.001$) [41]. Twelve-hour serial spirometry was also conducted for all patients in the ILLUMINATE study, and significant improvements were observed in FEV_1 with QVA149 versus SFC at all timepoints on day 1 and weeks 12 and 26 [42].

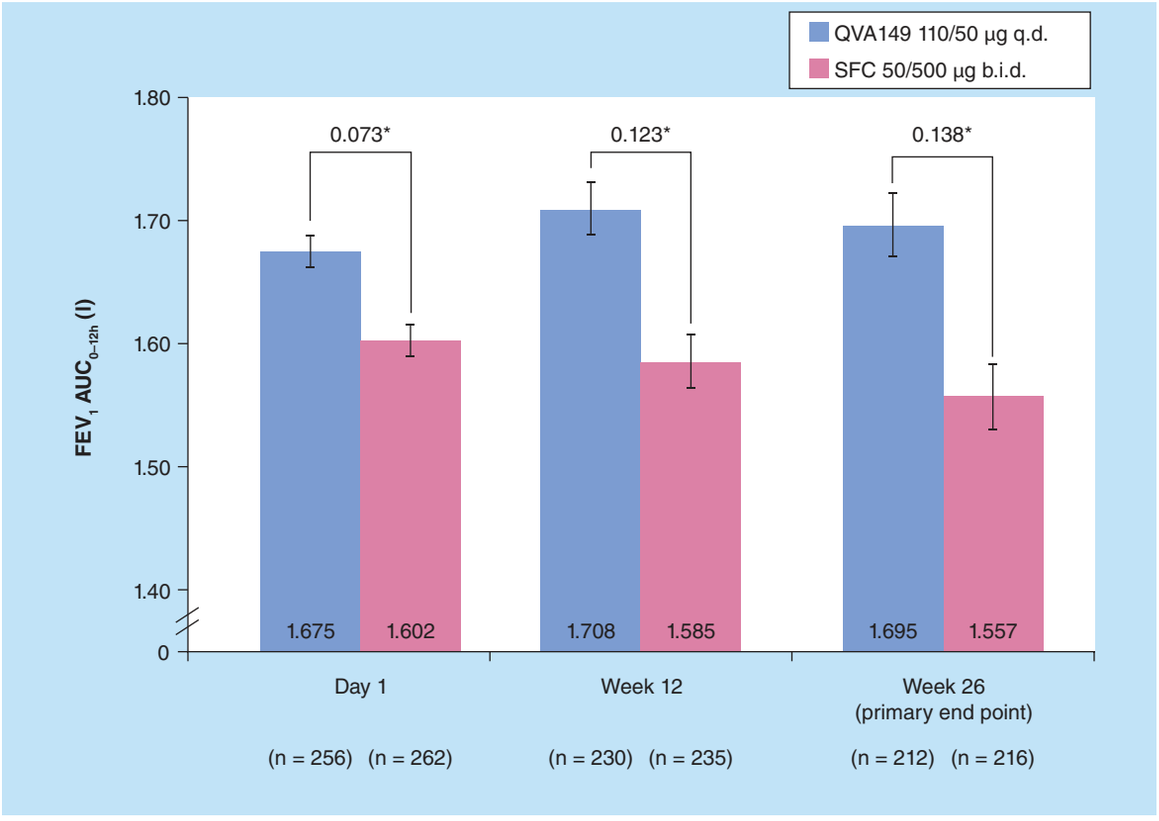

Figure 3. Forced expiratory volume in 1 s $AUC_{0–12h}$ at day 1, week 12 and week 26 in the ILLUMINATE study. Data are least-squares mean ± standard error. Numbers shown represent patient number per treatment group at each timepoint. *p < 0.0001 for comparisons between QVA149 and SFC.
b.i.d.: Twice daily; FEV_1: Forced expiratory volume in 1 s; SFC: Salmeterol/fluticasone propionate; q.d.: Once daily.
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In the SHINE and ILLUMINATE studies, QVA149 demonstrated a rapid onset of bronchodilator effect compared with placebo, glycopyrronium, tiotropium and SFC at day 1 (Supplementary Table 5), with treatment differences in FEV_1 at 5 min post-dose of 130 ml (95% CI: 110–140), 40 ml (95% CI: 30–50), 70 ml (95% CI: 60–80) and 81 ml (95% CI: 64–98), respectively (all p < 0.001) and at 30 min post-dose of 200 ml (95% CI: 180–220), 40 ml (95% CI: 20–50), 68ml (95% CI: 47–88) and 75 ml (95% CI: 54–97), respectively (all p < 0.001) [41,42]. QVA149 also significantly improved FEV_1 compared with indacaterol at 30 min post-dose on day 1 (LSM treatment difference 50 ml [95% CI: 30–60]; p < 0.001) [41]. The rapid onset of bronchodilation observed with QVA149 was sustained throughout the studies; FEV_1 significantly improved with QVA149 versus placebo, both monocomponents and tiotropium (SHINE) and versus SFC (ILLUMINATE) at 5 and 30 min post-dose on weeks 12 and 26 [41,42]. QVA149 also demonstrated a rapid onset of bronchodilation in the BLAZE study, with significant improvements in FEV_1 versus placebo and tiotropium at 5 and 30 min post-dose on day 1 and at week 6 (Supplementary Table 5) [47].

Lung function improvements have also been observed with umeclidinium/vilanterol 62.5/25 µg (Table 3). Umeclidinium/vilanterol significantly improved predose trough FEV_1, peak FEV_1 and FEV_1 $AUC_{0–6h}$ at week 24 compared with placebo in study DB2113373 (LSM treatment difference 167 ml [95% CI: 128–207], 224 ml [95% CI: 182–267] and 242 ml [95% CI: 202–282], respectively; all p < 0.001) [38]. Significant improvements in these measures were also observed with umeclidinium/vilanterol compared with umeclidinium and vilanterol in study DB2113373 [38] and compared with vilanterol and blinded tiotropium in study DB2113360 [50,56]. In study DB2113373, umeclidinium/vilanterol significantly improved trough FEV_1 on day 2 and improvements were sustained throughout the study versus placebo (p < 0.001 at all timepoints) and monocomponents (p ≤ 0.006 at all timepoints, except versus umeclidinium at day 112, which was not significant) (Figure 5) [38,57]. A greater proportion of patients achieved an increase in trough FEV_1 at week 24 from baseline >100 ml with umeclidinium/vilanterol compared with placebo and vilanterol (Supplementary Table 6) [38]. In the same

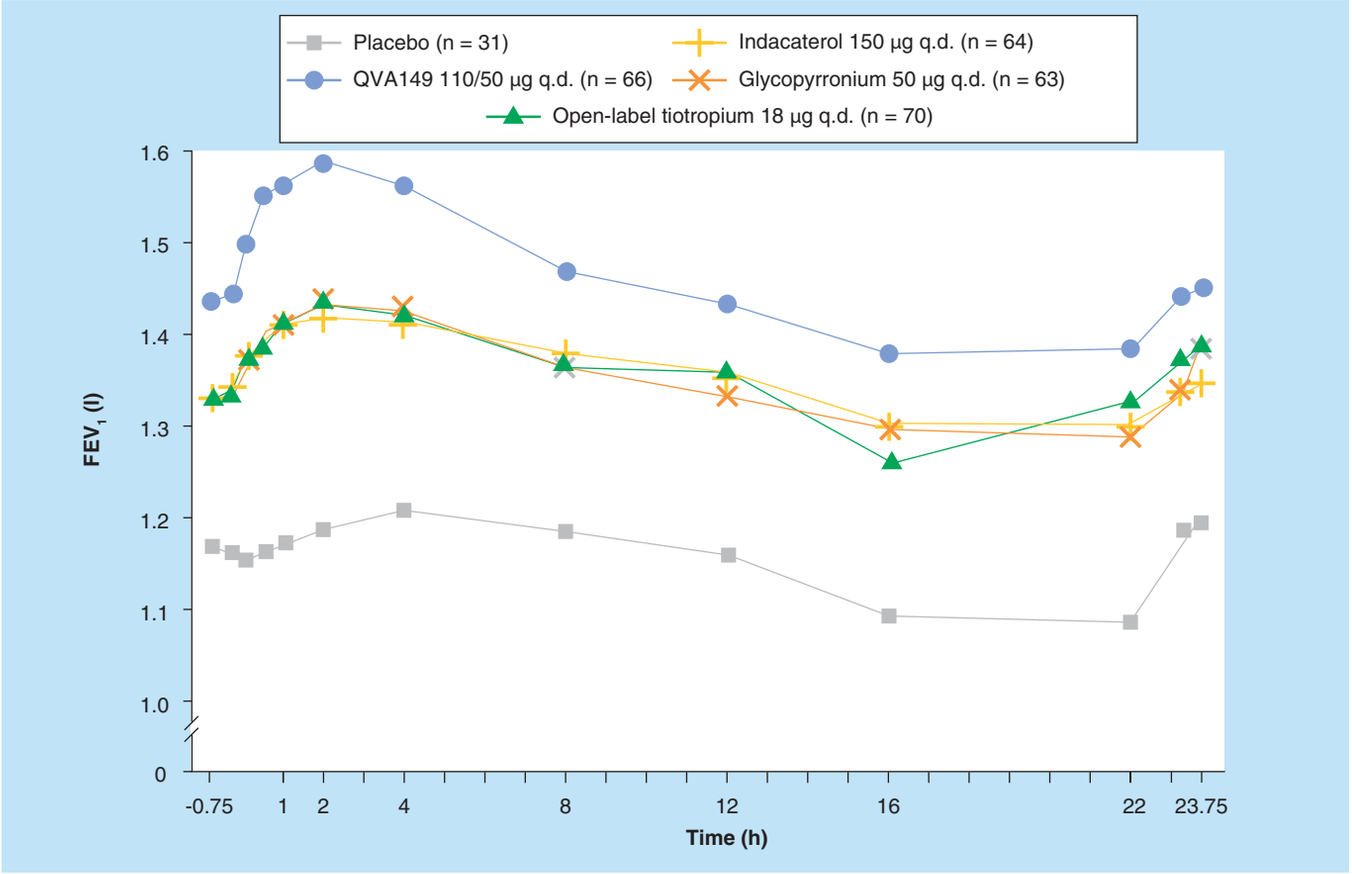

Figure 4. Serial spirometry at week 26 in the SHINE study. Data are least-squares mean. Analysis was conducted in a subset of patients (n = 294).
FEV_1: Forced expiratory volume in 1 s; n: Number per treatment group in the serial spirometry subset of the full analysis set; q.d.: Once daily.
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study, serial spirometry was conducted in a subpopulation of 197 patients for 24 h at day 1 and week 24 (Figure 6) [38]. Umeclidinium/vilanterol treatment resulted in sustained improvements in FEV_1 over 24 h compared with placebo, and increases in FEV_1 were numerically greater with umeclidinium/vilanterol compared with its monocomponents at almost all timepoints, with the exception of some of the earliest timepoints on day 1 [38,57].

In the umeclidinium/vilanterol primary efficacy and exercise endurance studies, a closed statistical testing hierarchy was used to control multiplicity across treatment comparisons and primary and secondary end points; statistical tests were performed in a predefined order and statistical significance was required in each test to draw inference from subsequent comparisons [57]. Statistical significance was not achieved at all points in the hierarchy for one of the primary efficacy studies (DB2113374) and one of the exercise endurance studies (DB2114417). In study DB2113374, comparisons of umeclidinium/vilanterol 125/25 µg and 62.5/25 µg were not significant versus umeclidinium 125 µg for trough FEV_1 [51]. This meant that although comparisons of umeclidinium/vilanterol with tiotropium for trough FEV_1 and comparisons of umeclidinium/vilanterol with umeclidinium 125 µg and tiotropium for FEV_1 $AUC_{0–6h}$ and peak FEV_1 achieved p-values of < 0.01 and < 0.05, respectively, the p-values for these comparisons were nominal [51,56,57]. In study DB214417, comparisons of umeclidinium/vilanterol with placebo, umeclidinium and vilanterol for trough FEV_1 at week 12 achieved p-values < 0.001; however, these were considered nominal because the first comparison in the testing hierarchy (3-h post-dose exercise endurance time at week 12 for umeclidinium/vilanterol versus placebo) did not achieve statistical significance [57]. However, trough FEV_1 improved significantly with umeclidinium/vilanterol versus placebo, umeclidinium and vilanterol at week 12 in the exercise endurance study DB2114418 [52,57].

Study DB2116133 evaluated lung function with umeclidinium/vilanterol 62.5/25 µg in patients

Table 3. Treatment difference with umeclidinium/vilanterol compared with placebo, monocomponents and standard of care, tiotropium: lung function.

Study	Comparator arm[†] (n)	Trough FEV_1, ml (95% CI)[‡]	Peak FEV_1, ml, week 24 (95% CI)	FEV_1 $AUC_{0–6h}$, ml, week 24 (95% CI)
UMEC/VI 62.5/25 µg q.d. vs placebo				
3373	280	**167 (128–207)***	224 (182–267)*	242 (202–282)*
4417	170	**211 (172–249)*,§**	NR	NR
4418	151	**243 (202–284)***	NR	NR
UMEC/VI 62.5/25 µg q.d. vs UMEC 62.5 µg q.d.				
3373	418	**52 (17–87)****	94 (57–132)*	92 (56–127)*
4417	49	**124 (67–181)*,§**	NR	NR
4418	40	**99 (41–157)***	NR	NR
UMEC/VI 62.5/25 µg q.d. vs UMEC 125 µg q.d.				
3374	222	**22 (-27–72)**[NS]**	67 (18–117)**,§	70 (24–117)**,§
UMEC/VI 62.5/25 µg q.d. vs VI 25 µg q.d.				
3373	421	**95 (60–130)***	116 (78–153)*	120 (84–155)*
3360	205	**90 (39–142)***	88 (35–142)**	77 (25–128)**
4417	76	**111 (62–161)*,§**	NR	NR
4418	64	**132 (81–183)***	NR	NR
UMEC/VI 62.5/25 µg q.d. vs tiotropium 18 µg q.d.				
3360	203	**90 (39–141)***	72 (19–125)**	74 (22–125)**
3374	215	**60 (10–109)***,§**	93 (44–142)*,§	96 (50–142)*,§

Values are mean treatment differences. Bold text indicates primary end points.
*p < 0.001; **p < 0.01; ***p < 0.05.
[†]UMEC/VI n = 413 (3373), 207 (3360), 217 (3374), 152 (4417) and 130 (4418).
[‡]At week 24 in 3373, 3374 and 3360, at week 12 in 4417 and 4418.
[§]p-values are nominal for this comparison according to the terms of the testing hierarchy for the study.
FEV_1: Forced expiratory volume in 1 s; NR: Not reported (analysis was not performed or data have not been published); NS: Not statistically significant; OR: Odds ratio; q.d.: Once daily; UMEC/VI: Umeclidinium/vilanterol.
Data taken from [38,50,51,52,56,57].

who respond to either umeclidinium 62.5 µg or vilanterol 25 µg to determine whether umeclidinium/vilanterol provided additional benefit [54]. Significantly greater improvements in FEV_1 $AUC_{0–6h}$ were observed in responders to umeclidinium or vilanterol with UMEC/VI compared with umeclidinium or vilanterol alone [54]. Nonresponders to umeclidinium or vilanterol and the overall intent-to-treat population also showed significant improvements in FEV_1 $AUC_{0–6h}$ with umeclidinium/vilanterol compared with either monocomponent alone [54].

Umeclidinium/vilanterol demonstrated rapid onset of efficacy compared with placebo at 15 min post-dose on day 1 and at all subsequent timepoints (30 min and 1, 3 and 6 h) in study DB2113373 [38,57]; similar results were obtained at days 28, 84, and 168 [57]. Statistically significant improvements were also observed with umeclidinium/vilanterol versus umeclidinium and vilanterol after 3 h on day 1, and at all timepoints on day 28, day 84 and day 168 [57]. The median time to onset (defined as a post-dose FEV_1 ≥100 ml above baseline) was 27 min during 0–6 h post dose on day 1 with umeclidinium/vilanterol, 31 min with vilanterol and 56 min with umeclidinium [38].

Lung volumes

Lung volume measurements can provide information on hyperinflation and airway resistance in patients with COPD. In the BRIGHT study, secondary end points included dynamic inspiratory capacity (IC) during exercise (at isotime) and trough IC, as well as functional residual capacity (FRC), residual volume (RV), slow vital capacity (SVC) and specific airway conductance (SGaw), determined by body plethysmography [43]. QVA149 was associated with significant improvements in dynamic IC and trough IC versus placebo (LSM treatment differences 320 ml [95% CI: 230–400] and 190 ml [95% CI: 90–290], respectively; p < 0.001) and tiotropium (140 ml [95% CI: 50–220] and 150 ml [95% CI: 60–250]; p < 0.01) at day 21 [43].

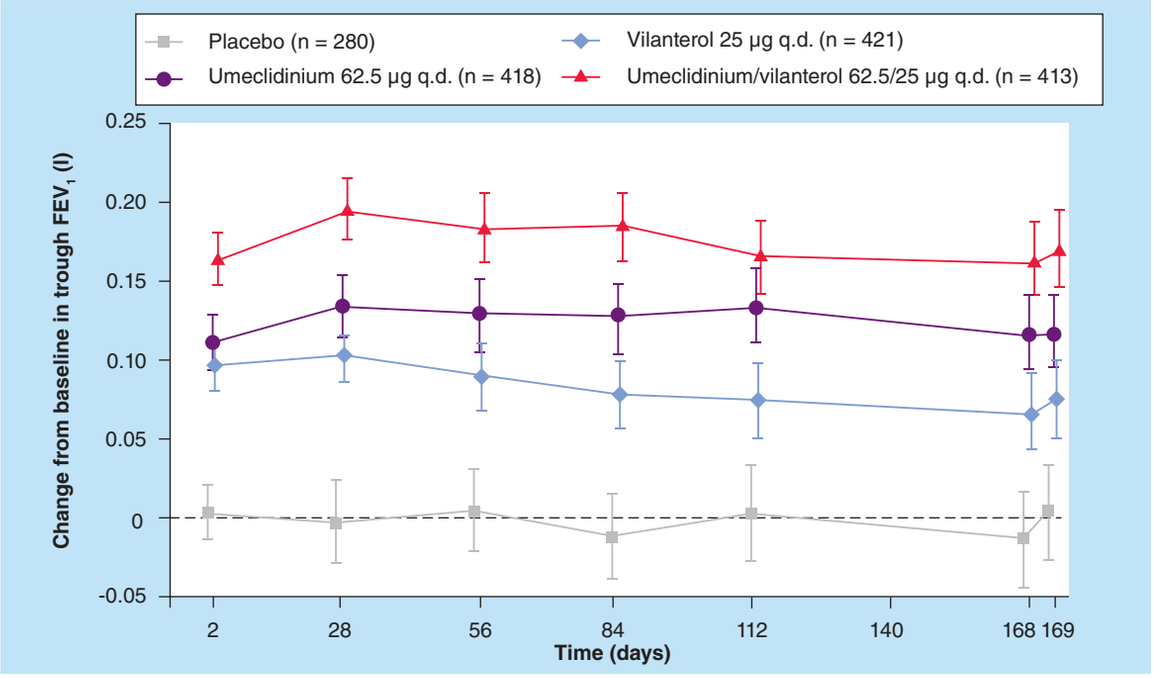

Figure 5. Change from baseline in trough forced expiratory volume in 1 s over the 24-week treatment period in study DB2113373. Data are least-squares mean ± 95% CI.
FEV_1: Forced expiratory volume in 1 s; q.d.: Once daily.
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Body plethysmography measurements also indicated a reduction in lung hyperinflation and airway resistance with QVA149: at days 1 and 21 significant improvements in FRC, RV, SVC and SGaw at 5, 15 and 60 min post dose were observed with QVA149 versus placebo. Significant improvements in SVC and SGaw were also observed for QVA149 versus tiotropium at some of the timepoints [43].

In the two umeclidinium/vilanterol exercise endurance studies, secondary end points included measures of lung volume: IC, FRC and RV [52]. Umeclidinium/vilanterol demonstrated significant improvements in trough and 3-h post-dose IC, FRC and RV compared with placebo at week 12 in study DB2114418 but not DB2114417 [52]. There are currently no data available on the effect of umeclidinium/vilanterol on dynamic hyperinflation; all reported measurements of hyperinflation were taken at rest.

Dyspnea

In the SHINE and ILLUMINATE studies, QVA149 significantly improved the Transition Dyspnea Index (TDI) total score and significantly increased the proportion of patients achieving the minimal clinically important difference (MCID) of at least 1 unit improvement in TDI score [58] from baseline compared with placebo, open-label tiotropium and SFC at week 26 (Table 4 & Supplementary Table 4) [41,42].

In the SHINE study, significantly greater proportions of patients also achieved improvements in TDI total score ≥2 units and ≥3 units at week 26 with QVA149 compared with placebo and tiotropium [41]. Improvements in TDI total score observed with QVA149 versus the monocomponents were not statistically significant at week 26; however, a significant improvement was observed with QVA149 compared with glycopyrronium at week 12 [41]. In the BLAZE study, QVA149 significantly improved the self-administered computerized TDI total score (the primary end point) and the proportion of patients who achieved the MCID with QVA149 versus placebo and blinded tiotropium [47].

Umeclidinium/vilanterol 62.5/25 µg significantly improved TDI total score and increased the proportion of patients who achieved the MCID compared with placebo in study DB2113373 (Table 5 & Supplementary Table 6) [38]. Improvements in TDI total score were not significant with umeclidinium/vilanterol versus the monocomponents; however, the proportion of patients who achieved the MCID was significantly increased with umeclidinium/vilanterol compared with vilanterol [38]. TDI total score did not improve with umeclidinium/vilanterol compared with either monocomponent or tiotropium in a pooled analysis of the active comparator studies DB2113360 and DB2113374 [59], nor were there improvements in the proportion of patients

who achieved the MCID in TDI total score in the individual studies [50,51].

Health status

In the SHINE study, QVA149 significantly improved the St George's Respiratory Questionnaire (SGRQ) total score versus placebo and tiotropium at week 26 (Table 4) [41]. SGRQ score was also significantly improved with QVA149 versus glycopyrronium and tiotropium at each timepoint assessed over 64 weeks in the SPARK study [45]. In the ILLUMINATE study, both QVA149 and SFC showed an improvement in SGRQ total score at week 26; the between-treatment group difference was not statistically significant [42]. The proportion of patients achieving the MCID of at least 4 units improvement in SGRQ total score [60] from baseline was significantly greater with QVA149 versus tiotropium at week 26 in the SHINE study (Supplementary Table 4) [41]. In addition, a significantly greater proportion of patients achieved an improvement in SGRQ total score ≥8 units with QVA149 compared with placebo, glycopyrronium and tiotropium at week 26 [41]. In the SPARK study, the proportion of patients achieving the MCID was significantly higher with QVA149 compared with glycopyrronium and tiotropium up to week 52; however, the difference just failed to achieve statistical significance at week 64 ($p = 0.055$ and $p = 0.051$ vs glycopyrronium and tiotropium, respectively) [45].

SGRQ total score significantly improved and the proportion of patients who achieved the MCID increased with umeclidinium/vilanterol compared with placebo at week 24 in study DB2113373 (Table 5 & Supplementary Table 6) [38]. However, no significant improvements in health status were observed versus the monocomponents or tiotropium in any study [38,50,51].

Cross study comparisons need to be viewed with caution owing to differences between the statistical modeling utilized. For example, when SGRQ data from the SHINE study are analyzed using the statistical model employed in the DB2113373 study (with covariates for treatment, baseline SGRQ score, baseline smoking status, baseline inhaled corticosteroid [ICS] use, region, visit, visit–baseline interaction and visit–treatment interaction) the treatment difference with QVA149 versus placebo increases from -3.99 to -4.61 at week 12 and from -3.01 to -3.55 at week 26 [Novartis, Unpublished Data]. It should also be noted that the improvement in SGRQ in the placebo-treated patients in the SHINE study was much greater than that in study DB2113373, reducing the difference measured versus placebo.

Patient symptoms

COPD symptoms were improved with QVA149 treatment (Table 4 & Supplementary Table 7). In the SHINE study, significant increases over 26 weeks were observed with QVA149 in nights with no night-time awakenings (versus placebo and glycopyrronium), in

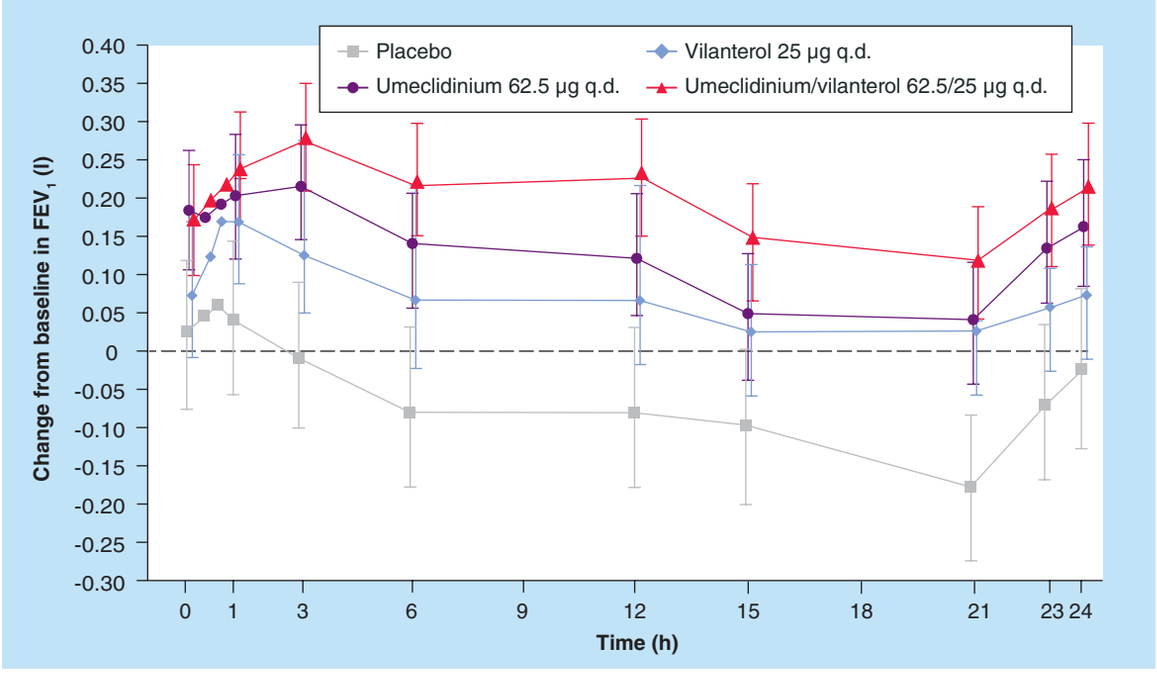

Figure 6. Serial spirometry at week 24 in study DB2113373. Data are least-squares mean ± 95% CI. Analysis was conducted in a subset of patients (n = 197).
FEV_1: Forced expiratory volume in 1 s; q.d.: Once daily.
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Table 4. Treatment difference with QVA149 compared with placebo, monocomponents and standards of care, tiotropium and salmeterol/fluticasone propionate: patient-reported outcomes.

Study	Comparator arm (n)[†]	Dyspnea, TDI total score (95% CI)[‡]	Health status, SGRQ total score (95% CI)[‡]	Daily total symptom score (95% CI)[§]	Rescue medication use, puffs/day (95% CI)[§]	Exacerbations (annual rate ratio)[§]	
						Moderate or severe exacerbations (95% CI)	All exacerbations (95% CI)
QVA149 110/50 µg q.d. vs placebo							
SHINE	232	1.09 (0.61–1.57)*	-3.01 (-5.05 to -0.97)**	-0.67 (-0.96 to -0.39)*	-0.96 (-1.29 to -0.62)*	0.57 (0.41–0.79)*	NR
BLAZE	218	**1.37 (0.95–1.79)***,[¶]	NR	-0.72 (-0.94 to -0.49)*	-1.43 (-1.72 to -1.13)*	NR	NR
QVA149 110/50 µg q.d. vs Ind 150 µg q.d.							
SHINE	476	0.26 (-0.11–0.63)[NS]	-1.09 (-2.68–0.5)[NS]	-0.13 (-0.36–0.1)[NS]	-0.30 (-0.57 to -0.03)***	NR	NR
QVA149 110/50 µg q.d. vs Gly 50 µg q.d.							
SHINE	473	0.21 (-0.17–0.58)[NS]	-1.18 (-2.78–0.42)[NS]	-0.26 (-0.49 to -0.03)***	-0.66 (-0.93 to -0.39)*	NR	NR
SPARK	739	NR	-2.07 (-3.57 to -0.58)**	-0.37 (-0.55 to -0.19)*	-0.81 (-1.07 to -0.56)*	**0.88 (0.77–0.99)*****	0.85 (0.77–0.94)**
QVA149 110/50 µg q.d. vs Ind 150 µg + Gly 50 µg q.d.[#]							
BEACON	97	NR	NR	0.07 (-0.24–0.39)[NS]	-0.04 (-0.35–0.28)[NS]	NR	NR
QVA149 110/50 µg q.d. vs tiotropium 18 µg q.d.[††]							
SHINE	480	0.51 (0.14–0.88)**	-2.13 (-3.72 to -0.54)**	-0.24 (-0.46 to -0.01)***	-0.54 (-0.81 to -0.27)*	NR	NR
BLAZE	220	0.49 (0.07–0.91)***,[¶]	NR	-0.03 (-0.26–0.19)[NS]	-0.45 (-0.74 to -0.16)**	NR	NR
SPARK	737	NR	-2.69 (-4.17 to -1.21)*	-0.44 (-0.62 to -0.26)*	-0.76 (-1.01 to -0.5)*	0.90 (0.79–1.02)[NS]	0.86 (0.78–0.94)**
QVA149 110/50 µg q.d. vs SFC 50/500 µg b.i.d.							
ILLUMINATE	264	0.76 (0.26–1.26)**	-1.24 (-3.33–0.85)[NS]	-0.05 (-0.29–0.2)[NS]	-0.39 (-0.71 to -0.06)***	0.80 (0.41–1.56)[NS‡‡]	0.69 (0.44–1.07)[NS‡‡]

Values are mean treatment differences with the exception of rate ratios. Bold text indicates primary end points.
*p < 0.001; **p < 0.01; ***p < 0.05.

[†]QVA149 n = 474 (SHINE), 223 (BLAZE), 729 (SPARK), 84 (BEACON) and 258 (ILLUMINATE).

[‡]At week 26 in SHINE and ILLUMINATE, at week 6 in BLAZE and at week 64 in SPARK.

[§]Over treatment period (26 weeks in SHINE and ILLUMINATE, 6 weeks in BLAZE, 64–76 weeks in SPARK and 4 weeks in BEACON).

[¶]Self-administered computerized total score.

[#]Free combination.

[††]Open-label in SHINE and SPARK, blinded in BLAZE.

[‡‡]*Post hoc* analysis.

b.i.d.: Twice daily; Gly: Glycopyrronium; Ind: Indacaterol; NR: Not reported (analysis was not performed or data have not been published); NS: Not statistically significant; q.d.: Once daily; SGRQ: St George's respiratory questionnaire; SFC: Salmeterol/fluticasone propionate; TDI: Transition Dyspnea Index.
Data taken from [41,42,45,47,48,99,100] and [Novartis, Unpublished Data].

percentage of days with no daytime symptoms (versus placebo), in percentage of days patients were able to perform usual daily activities (versus placebo, the monocomponents and tiotropium) and daily total symptom score (versus placebo, glycopyrronium and tiotropium) [41]. In the SPARK study, significant improvements were observed over 64–76 weeks in the percentage of nights with no night-time awakenings, percentage of days with no daytime symptoms and daily total symptom score with QVA149 versus glycopyrronium and tiotropium [Novartis, Unpublished Data]. QVA149 also significantly improved the percentage of days patients were able to perform usual daily activities versus tiotropium in SPARK [Novartis, Unpublished Data]. QVA149 significantly increased the percentage of days with no daytime symptoms versus SFC over 26 weeks (ILLUMINATE) [42]. Changes in patient symptoms (including daily total symptom score) during 6 weeks of treatment with QVA149 were significant versus placebo but not compared with tiotropium in the BLAZE study [47]. In the BEACON study, patients treated with QVA149 and those treated with the free combination of indacaterol and glycopyrronium experienced similar changes in daily total symptom score during 4 weeks of treatment [48]. No symptom score data are available for the umeclidinium/vilanterol combination.

Rescue medication use

Daily rescue medication use was significantly reduced with QVA149 versus placebo, monocomponents, tiotropium and SFC (Table 4) [41,42,45,47]. The percentage of days with no rescue medication use also significantly increased with QVA149 compared with placebo, glycopyrronium and tiotropium (Supplementary Table 7) [41,45,47]. In addition, the reductions in use of rescue medication observed with QVA149 were similar to those observed with the free combination of indacaterol and glycopyrronium in the BEACON study [48].

Umeclidinium/vilanterol treatment also led to improvements in rescue medication use (Table 5). Daily use of rescue medication was significantly reduced compared with placebo and umeclidinium in study DB2113373 [38], and compared with

Table 5. Treatment difference with umeclidinium/vilanterol compared with placebo, monocomponents and standard of care, tiotropium: patient-reported outcomes.

Study	Comparator arm (n)†	Dyspnea, TDI total score, week 24 (95% CI)	Dyspnea, SOBDA score, week 24 (95% CI)	Health status, SGRQ total score, week 24 (95% CI)	Rescue medication use, puffs/day, over 24 weeks (95% CI)	Time to first exacerbation, hazard ratio (95% CI)
UMEC/VI 62.5/25 µg q.d. vs placebo						
3373	280	1.2 (0.7–1.7)*	-0.17 (-0.26 to -0.08)*	-5.51 (-7.88 to -3.13)*	-0.8 (-1.3 to -0.3)**	0.5 (0.3–0.8)**
UMEC/VI 62.5/25 µg q.d. vs UMEC 62.5 µg q.d.						
3373	418	0.3 (-0.2–0.7)^{NS}	-0.08 (-0.16–0.01)^{NS}	-0.82 (-2.90–1.27)^{NS}	-0.6 (-1.0 to -0.1)***	NR
UMEC/VI 62.5/25 µg q.d. vs UMEC 125 µg q.d.						
3374	222	0.4 (-0.2–1.0)^{NS‡}	-0.10 (-0.21–0.01)^{NS}	-1.55 (-4.25–1.16)^{NS}	-0.6 (-1.2–0.0)^{NS}	NR
UMEC/VI 62.5/25 µg q.d. vs VI 25 µg q.d.						
3373	421	0.4 (-1.0–0.8)^{NS}	-0.03 (-0.11–0.05)^{NS}	-0.32 (-2.41–1.78)^{NS}	0.1 (-0.3–0.5)^{NS}	NR
3360	205	0.2 (-0.4–0.8)^{NS‡}	-0.02 (-0.14–0.10)^{NS}	1.42 (-1.46–4.30)^{NS}	-0.3 (-0.8–0.3)^{NS}	NR
UMEC/VI 62.5/25 µg q.d. vs tiotropium 18 µg q.d.						
3360	203	0.1 (-0.4–0.5)^{NS‡}	0 (-0.12–0.12)^{NS}	0.75 (-2.12–3.63)^{NS}	-0.7 (-1.2 to -0.1)***	NR
3374	215	0.1 (-0.4–0.5)^{NS‡}	-0.08 (-0.20–0.03)^{NS}	-0.17 (-2.85–2.52)^{NS}	-0.6^{NS}	NR

Values are mean treatment differences with the exception of hazard ratios.
*p < 0.001; **p < 0.01; ***p < 0.05.
†UMEC/VI n = 413 (3373), 207 (3360) and 217 (3374).
‡Pooled analysis of studies DB2113360 and DB2113374.
NR: Not reported (analysis was not performed or data have not been published); NS: Not statistically significant; q.d.: Once daily; SGRQ: St George's respiratory questionnaire; SOBDA: Shortness of breath with daily activity; TDI: Transitional Dyspnea Index; UMEC/VI: Umeclidinium/vilanterol.
Data taken from [38,50,51,56,57,59]

tiotropium in study DB2113360 [50].

Exacerbations

In the SPARK study, QVA149 significantly reduced the rate of moderate (treated with systemic corticosteroids or antibiotics or both) or severe exacerbations (requiring hospital admission or emergency treatment) during the 64–76-week treatment period (the primary end point) by 12% compared with glycopyrronium (rate ratio 0.88 [95% CI: 0.77–0.99]; p = 0.038; Table 4) [45]. Compared with tiotropium, the rate of moderate or severe exacerbations was reduced by 10% with QVA149, although this difference was not statistically significant (rate ratio: 0.90 [95% CI: 0.79–1.02]; p = 0.096) [45]. The rate of all COPD exacerbations (mild [self-managed by the patient], moderate and severe) was also reduced with QVA149 by 15% compared with glycopyrronium (rate ratio: 0.85 [95% CI: 0.77–0.94]; p = 0.0012) and by 14% compared with tiotropium (rate ratio: 0.86 [95% CI: 0.78–0.94]; p = 0.0017) [45]. The rates of exacerbations that led to hospitalization or emergency treatment (classified as severe) in the SPARK study were low in all treatment groups with no significant difference observed between QVA149 and either comparator (Supplementary Table 7) [45].

In a *post hoc* analysis of the ILLUMINATE study, the rate of moderate or severe exacerbations and the rate of all exacerbations were comparable in patients treated with QVA149 and in those treated with SFC during the 26-week treatment period [42].

The impact of umeclidinium/vilanterol on COPD exacerbations was explored as an additional end point in the 24-week primary efficacy studies, although these studies were not specifically designed to evaluate the effect of treatments on exacerbations, and patients were withdrawn if an exacerbation occurred [57]. According to analysis of time to first exacerbation (defined as an acute worsening of symptoms of COPD requiring emergency treatment, hospitalization, or the use of systemic corticosteroids or antibiotics), umeclidinium/vilanterol significantly reduced the risk of exacerbation by 50% compared with placebo (hazard ratio: 0.5 [95% CI: 0.3–0.8]; p < 0.001; Table 5) [38]. In the active comparator studies, COPD exacerbations were observed in 7, 8 and 5% of patients treated with umeclidinium/vilanterol, vilanterol and tiotropium, respectively (study DB2113360) [50], and in 12, 12 and 7% of patients treated with umeclidinium/vilanterol, umeclidinium 125 µg and tiotropium, respectively (study DB2113374) [51]. An integrated analysis of the four primary efficacy studies showed that the risk of exacerbations was not different with umeclidinium/vilanterol versus tiotropium [56].

Exercise measurements

The effect of combining bronchodilators on exercise performance was investigated in both the QVA149 and umeclidinium/vilanterol clinical trial programs. Exercise endurance time (EET) during a sub-maximal exercise tolerance test via constant load cycle ergometry at day 21 was the primary end point of the BRIGHT trial [43]. EET was significantly increased by 59.5 s (95% CI: 17.7–101.3) with QVA149 versus placebo (p = 0.006); this improvement was of a similar magnitude to that observed with tiotropium versus placebo (66.3 s [95% CI: 24.8–107.7]; p = 0.002) [43].

In studies DB2114417 and DB2114418, the effects of UMEC/VI on EET were evaluated using the endurance shuttle walk test 3 h after dosing (the co-primary end point of both studies) [52]. EET was significantly improved with umeclidinium/vilanterol 62.5/25 µg compared with placebo in study DB2114418 (by 69.4 s; [95% CI: 24.5–114.4] p < 0.01) but not in study DB2114417 (treatment difference of 21.9 s [95% CI: -14.2–58.0]) [52].

Safety

The potential association between bronchodilators and cardio- and cerebro-vascular (CCV) morbidity and mortality is of concern; the use of anticholinergics and β_2-agonists has been linked with CCV events in patients with COPD [61,62]. In addition, an independent systematic review and meta-analysis of 12-month randomized controlled trials found a 52% increase in mortality risk associated with tiotropium delivered using a mist inhaler (Respimat®) [63]. However, in the recently completed large TIOSPIR® trial, tiotropium Respimat (2.5 or 5 µg) was found to be noninferior to tiotropium (18 µg) administered via the HandiHaler® device for risk of death [64]. When combining bronchodilators, therefore, not only does the efficacy of the combination have to be taken into consideration, but also the associated safety profile.

The monocomponents of QVA149, glycopyrronium and indacaterol, are approved for use as monotherapy in COPD and have well-characterized safety profiles. Glycopyrronium showed no evidence of being associated with adverse cardiovascular effects [65] and indacaterol has an overall CCV safety profile similar to that of placebo [66,67]. The eligibility criteria used in the QVA149 IGNITE studies were comparable to the criteria used in the pivotal studies for glycopyrronium and indacaterol, resulting in similar patient populations across the three clinical development programs [28–30,68–73].

In the SHINE study, the overall incidence of adverse events (AEs) over 26 weeks was similar between QVA149 (55.1%), placebo (57.8%), indacaterol (61.1%), glyco-

pyrronium (61.3%) and tiotropium (57.3%) groups, with COPD worsening reported most frequently [41]. The rate of treatment discontinuation as a result of AEs in the QVA149 group was 1.3%, lower than placebo (4.3%) and the active comparators (2.1–5.0%) [41]. Serious AEs (SAEs) also occurred less frequently in the QVA149 group compared with placebo (4.6 and 5.6%, respectively) [41]. Seven deaths occurred during the SHINE study, none of which were considered by the investigator to be related to the study drug [41]. The occurrence of CCV SAEs was low across treatment groups; no CCV SAEs were reported in the QVA149 group and few were reported and adjudicated in the other treatment groups (0.4–1.5%) [41].

The long-term safety of QVA149 was investigated for 52 weeks in the ENLIGHTEN study [44]. The overall incidence of AEs was comparable between QVA149 and placebo groups (57.8 and 56.6%, respectively), and COPD worsening was the most frequently reported AE (28.0 and 25.7%) [44]. AEs that led to study drug discontinuation were also reported in similar proportions in the QVA149 and placebo groups (5.8 and 6.2%, respectively) [44]. SAEs occurred in 16.4% of patients in the QVA149 group and 10.6% of the placebo group [44]. CCV AEs were reported by 5.3% of patients in the QVA149 group and 2.7% of patients in the placebo group. The incidence of CCV SAEs, reported in five patients in the QVA149 group (2.2%) and none in the placebo group, was not significantly different between the two groups (odds ratio: 3.43 [95% CI: 0.46–Inf]; p = 0.258) [44]. There were five deaths during the treatment period and within 30 days of the last treatment (four in the QVA149 group and one in the placebo group) [44]. None of the deaths were thought to be related to the study drug, as determined by the investigator, and the difference in time to death between treatment groups was not statistically significant (hazard ratio: 1.7 [95% CI: 0.19–15.36]; p = 0.638). The numerical imbalance in the rates of SAEs and deaths between the QVA149 and placebo groups is likely to be owing to demographic imbalance between the groups; at baseline, more patients had severe COPD, used ICS and had a history of myocardial infarction, stroke and diabetes mellitus in the QVA149 group [44]. Long-term safety data for QVA149 are also available from the SPARK study, in which 729 patients with severe-to-very severe COPD were treated with QVA149 for up to 76 weeks [45]. The overall safety profile of QVA149 was found to be similar to that of glycopyrronium and tiotropium, and all treatments were well tolerated [45].

In a pooled analysis of 6-month safety data from three pivotal Phase III studies (SHINE, ILLUMINATE and ENLIGHTEN) and a safety study in Japanese patients (ARISE), the overall proportion of patients with any AE in the QVA149 group (51.5%) was lower compared with the indacaterol, glycopyrronium, open-label tiotropium and SFC groups (56.8–61.3%; Table 6) [74]. The incidence of any SAE was similar between the QVA149 and all other active treatment groups (5.3–6.1%) apart from the tiotropium group, in which the rate of SAEs was slightly lower (3.9%) [74]. CCV events occurred in 1.8% of patients in the QVA149 group, similar to the tiotropium group

Table 6. Pooled 6-month safety data for placebo, QVA149, monocomponents and standards of care, tiotropium and salmeterol/fluticasone propionate†.

Regimen	Patients (n)	Total AEs	AEs leading to permanent discontinuation of study drug	Total SAEs	Deaths	CCV AEs	CCV SAEs	MACE, total	Atrial fibrillation/ flutter events
QVA149 110/50 μg q.d.	1076	593 (55.1)	37 (3.4)	59 (5.5)	3 (0.3)	19 (1.8)	6 (0.6)	3 (0.3)	9 (0.8)
Placebo	345	190 (55.1)	16 (4.6)	19 (5.5)	0	9 (2.6)	1 (0.3)	0	2 (0.6)
Indacaterol 150 μg q.d.	476	291 (61.1)	24 (5.0)	26 (5.5)	2 (0.4)	12 (2.5)	4 (0.8)	2 (0.4)	7 (1.5)
Glycopyrronium 50 μg q.d.	473	290 (61.3)	14 (3.0)	29 (6.1)	1 (0.2)	14 (3.0)	6 (1.3)	3 (0.6)	10 (2.1)
Tiotropium 18 μg q.d.	519	295 (56.8)	10 (1.9)	20 (3.9)	3 (0.6)	9 (1.7)	3 (0.6)	3 (0.6)	7 (1.3)
SFC 50/500 μg b.i.d.	264	159 (60.2)	27 (10.2)	14 (5.3)	1 (0.4)	6 (2.3)	3 (1.1)	1 (0.4)	7 (2.7)

†Pooled 6-month safety data from SHINE, ILLUMINATE, ENLIGHTEN and ARISE studies. All values are n (%).
AE: Adverse event; b.i.d.: Twice daily; CCV: Cardio- and cerebro-vascular; MACE: Major adverse cardiac event; q.d.: Once daily; SAE: Serious adverse event; SFC: Salmeterol/fluticasone propionate.
Data taken from [74,75]. Adapted with permission from [74] © European Respiratory Society (2013).

(1.7%) and lower than that in the placebo and other active comparator groups (2.3–3.0%) [74]. The incidence of CCV SAEs was low in the QVA149 group (0.6%) and similar to that observed in the other active treatment groups (0.6–1.3%) [74].

Umeclidinium 62.5 µg monotherapy was well tolerated in a 12-week study, compared with placebo, and there were no notable differences in safety profile between the 62.5 and 125 µg doses [39]. Vilanterol 25 µg was also found to have a favorable safety profile [40]. However, neither monocomponent is currently approved as a monotherapy.

In study DB2113373, the incidences of AEs over 24 weeks in the umeclidinium/vilanterol, placebo, umeclidinium and vilanterol groups were 51, 46, 52 and 48%, respectively (Table 7) [38]. AEs that led to study withdrawal were reported in slightly fewer patients in the placebo group (3%) compared with the active treatment groups (6–8%), as were SAEs (3% vs 5–6%, respectively) [38]. The only SAE or AE (including both on- and post-treatment AEs) that led to withdrawal from the study in ≥1% of patients was related to COPD worsening. Nine deaths occurred in the DB2113373 study; three patients in the umeclidinium/vilanterol group (COPD exacerbation/respiratory failure, myocardial infarction and unknown cause), three in the umeclidinium group (COPD/acute respiratory failure, sudden death, and cholecystitis and peritonitis) and three in the vilanterol group (sudden death, COPD exacerbation and COPD exacerbation/renal failure) [38]. No clinically significant changes were observed for blood pressure, heart rate or QT interval [38]. In addition, no apparent treatment differences were observed for abnormal 12-lead electrocardiogram findings for any of the active treatments [38].

Long-term safety data for umeclidinium/vilanterol are only available for patients who received the higher 125/25 µg dose combination; in study DB2113359, 146 patients received umeclidinium/vilanterol 125/25 µg for at least 48 weeks [53,56]. Umeclidinium/vilanterol 125/25 µg was well tolerated during 12 months of treatment, and the incidence of AEs and SAEs in the active treatment groups (umeclidinium/vilanterol 125/25 µg and umeclidinium 125 µg) was similar to placebo (AEs: 52–58%, SAEs: 6–7%) [53]. The most common AE in all treatment groups was headache (8–11%), and fewer AEs leading to permanent discontinuation or withdrawal occurred in the umeclidinium/vilanterol 125/25 µg (8%) and umeclidinium 125 µg (9%) treatment groups compared with placebo (11%) [53]. Five deaths occurred during the study (four in the umeclidinium/vilanterol 125/25 µg group and one in the placebo group). None of the deaths were thought to be related to the study drug by the investigator.

In a pooled safety analysis of the 24-week primary efficacy trials, reported in the FDA briefing document, there was a slight imbalance in the overall proportion of patients with any AE between the umeclidinium/vilanterol treatment groups (53%) and placebo (48%) [56]. The proportion of patients with an SAE was 4% in the placebo group and 5–6% across all active treatment groups [56]. A MACE analysis, performed on the pooled intent-to-treat population from all COPD studies with a treatment duration of at least 12 weeks, and an analysis of cardiovascular AEs of special interest performed on the pooled population from the primary efficacy trials both indicated a numerical imbalance favoring placebo over umeclidinium/vilanterol for events related to cardiovascular ischemia [56]. However, similar patterns were not observed for the long-term safety trial.

In conclusion, both QVA149 and umeclidinium/vilanterol were generally well tolerated. QVA149 had a favorable AE profile compared with placebo, the individual components and current standards of care, tiotropium and SFC [41,42,45,47]. No additional safety signals were observed with QVA149 compared

Table 7. 24-week safety data for placebo, umeclidinium/vilanterol, umeclidinium and vilanterol (study DB2113373).

Regimen	Patients (n)	On-treatment AEs	AEs leading to withdrawal/ discontinuation of study drug†	On-treatment SAEs	Fatal SAEs
UMEC/VI 62.5/25 µg q.d	413	212 (51)	23 (6)	21 (5)	3 (<1)
Placebo	280	130 (46)	9 (3)	9 (3)	0
Umeclidinium 62.5 µg q.d.	418	216 (52)	34 (8)	27 (6)	3 (<1)
Vilanterol 25 µg q.d.	421	204 (48)	24 (6)	24 (6)	3 (<1)

†Includes both on- and post-treatment AEs. All values are n (%).
AE: Adverse event; q.d.: Once daily; SAE: Serious adverse event; UMEC/VI: Umeclidinium/vilanterol.
Adapted with permission from [38] © Elsevier (2013).

with the monocomponents [74,75]. The safety profile of umeclidinium/vilanterol was consistent with that of the individual components with no evidence of additive adverse effects for the combination over the monocomponents [57].

Ongoing studies

There are several ongoing trials, which will provide further data on the safety and efficacy of combining bronchodilators in the treatment of COPD. For QVA149, these include three further trials in the IGNITE program: a long-term safety study versus blinded tiotropium and placebo over 52 weeks (RADIATE, formerly GLISTEN; NCT01610037) [76]; a comparison of the effect of QVA149 on exacerbations versus SFC over 52 weeks (FLAME; NCT01782326) [77]; and a 26-week study, which will investigate the efficacy (noninferiority) and safety of QVA149 versus SFC in patients from Argentina, Brazil, Chile, China and Taiwan (LANTERN; NCT01709903) [78]. Additionally, preliminary results from a *post hoc* analysis of the SHINE data suggest that QVA149 can have a 'super bronchodilatory' effect, with a change from baseline in trough FEV_1 at week 26 of >300 ml in approximately one in four patients treated with QVA149 [Novartis, Unpublished Data]. Further analyses of such patients may be informative.

Data from a number of umeclidinium/vilanterol investigations are awaiting full publication; DB2113373 and DB2113361 are the only studies published in full [38,49]. A 24-week study was recently completed comparing the efficacy and safety of umeclidinium/vilanterol with tiotropium (NCT01777334; data are yet to be published) [55], and a 12-week study is ongoing, which will evaluate the effect of umeclidinium/vilanterol on lung function versus tiotropium in patients with COPD who remain symptomatic while treated with tiotropium (NCT01899742) [79]. In addition, three clinical trials are ongoing, which will compare the efficacy and safety of umeclidinium/vilanterol with SFC (NCT01817764, NCT01822899 and NCT01879410) [80–82]. The effect of umeclidinium/vilanterol on exacerbations as a primary end point in a long-term study in patients with a history of exacerbations is currently not under investigation.

Conclusions

QVA149 and umeclidinium/vilanterol have both demonstrated positive effects on bronchodilation compared with their respective monocomponents. Superior bronchodilation and improvements in clinical outcomes were observed with QVA149 compared with the monocomponents and current standards of care, tiotropium and SFC, as well as placebo [41–43,45,47]. Umeclidinium/vilanterol also demonstrated superior bronchodilation compared with placebo and tiotropium, and improvements in clinical outcomes were noted for umeclidinium/vilanterol compared with placebo [38,50–52]. Furthermore, there were no additional safety concerns observed with combinations of long-acting bronchodilators compared with the monocomponents [56,74,75]. QVA149 and umeclidinium/vilanterol are both administered once daily via a single inhaler; both once-daily dosing [83] and single-inhaler use [84] have been shown to result in higher adherence in patients with COPD, compared with other daily dosing schedules and the use of multiple inhalers.

Although benefits of QVA149 and umeclidinium/vilanterol compared with monocomponents and current standards of care were observed, few mean treatment differences in trough FEV_1, and none of the mean differences in TDI score or SGRQ score, achieved the MCID versus active comparators. However, experience with MCIDs has most often been in the context of placebo-controlled trials, where treatment differences can be large. A more appropriate method to assess the minimum worthwhile incremental advantage between active treatment regimens may therefore be to use a responder analysis to identify the additional proportion of patients who experience improvement at or above the MCID [85].

It is important to note that improvements in FEV_1 do not necessarily translate into improvements in symptoms, such as dyspnea, and an individual may experience a clinically important benefit based on one outcome but not others. In an analysis of the relationship between FEV_1 and patient-reported outcomes, a 100 ml increase in FEV_1 was associated with an improvement in TDI total score of 0.5, which falls short of the 1 unit MCID [86]. A similar result was found in a pooled analysis of three indacaterol studies: although a change in FEV_1 was significantly correlated with TDI score, the model-predicted increase in TDI total score for a 100 ml increase in FEV_1 was 0.46 [87]. Equally, not all dyspnea experienced by patients with COPD is caused by reduced FEV_1. Alternative potential causes of dyspnea include concomitant cardiac disease, pulmonary vascular disease, anemia, deconditioning, environmental hypoxia and behavioral factors such as anxiety disorders [88].

Given the positive results from clinical investigations with QVA149 and umeclidinium/vilanterol in patients with COPD, the positioning of LABA/LAMA fixed-dose combinations in current treatment guidelines and algorithms is a point of discussion. For patients who remain symptomatic with a single bronchodilator, should prescription of a LABA/LAMA be the next step? Many patients who are receiving treat-

ment continue to experience symptoms. For instance, most GOLD stage 2 patients in an analysis of the Optimum Patient Care Research Database remained symptomatic; 91.4% of patients had a Medical Research Council dyspnea scale score ≥2 and 95.0% had a COPD Assessment Test score ≥11 [89]. As demonstrated in the QVA149 trials, a LABA/LAMA can provide improvements in patient symptoms compared with a single bronchodilator alone [41,45]. In addition, the choice between a LABA/LAMA and a LABA/ICS should also be considered. LABA/ICS are recommended for use in patients who are at high risk of exacerbations (Groups C and D) in the GOLD 2014 strategy document [1]. There are concerns surrounding the use of LABA/ICS in the treatment of COPD, namely the uncertainty around the contribution of ICS to the clinical efficacy of the combination [90,91] and risks associated with ICS use [91–93]. Combined bronchodilators can be at least as effective as LABA/ICS in the treatment of patients equivalent to GOLD Group B, as data from the ILLUMINATE study demonstrate [42]. QVA149 provided significant and clinically meaningful improvements in lung function and significant symptomatic benefits versus SFC in patients who were at low risk of exacerbation but had a high symptom burden [94]. The FLAME study, which will compare the effect of QVA149 on exacerbations versus SFC, will potentially help to clarify whether a dual bronchodilator can provide benefits to those who are at high risk [77].

Further data on the efficacy and safety of dual bronchodilators are required before changes in treatment recommendations can be considered. For instance, there is currently little information on the effects of dual bronchodilators on hospitalization rates and mortality, and the SPARK trial is presently the only study to have evaluated the effect of a LABA/LAMA compared with two marketed LAMAs (glycopyrronium and tiotropium) on exacerbations as the primary end point. Long-term studies are therefore required to explore the impact of dual bronchodilators on these outcomes in patients with COPD. It seems likely, however, that if bronchodilation can be optimized through combining bronchodilators, leading to improvements in patient symptoms and morbidity, dual bronchodilators will feature prominently in COPD treatment strategies and guidelines in the future.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: http://www.future-science.com/doi/full/10.4155/CLI.14.50

Additional supplementary material is available at: http://oernst.f5lvg.free.fr/liver/iron.html.

Financial & competing interests disclosure

D Banerji and R Fogel are employees of Novartis. K-M Beeh has received compensation for organizing or participating in advisory boards for Almirall Hermal, AstraZeneca, Boehringer

Executive summary

Background

- The administration of long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) in fixed-dose combinations is supported by both scientific rationale and the clinical efficacy of free combinations of LABAs and LAMAs and a fixed-dose combination of short-acting bronchodilators.
- Two LABA/LAMA fixed-dose combinations have recently been approved for use in the treatment of chronic obstructive pulmonary disease (COPD): QVA149 in Europe, Japan and a number of other countries, and umeclidinium/vilanterol in the USA.

Efficacy

- Considerable data from Phase III trials evaluating the efficacy and safety of QVA149 and umeclidinium/vilanterol have become available, which demonstrate improvements in lung function measures and patient-reported outcomes with the LABA/LAMA combinations.
- Superior bronchodilation and improvements in clinical outcomes were observed with QVA149 compared with placebo, its monocomponents and current standards of care tiotropium and salmeterol/fluticasone.
- Umeclidinium/vilanterol demonstrated superior bronchodilation compared with placebo, the monocomponents and tiotropium, and improvements in clinical outcomes were noted for umeclidinium/vilanterol compared with placebo.

Safety

- No additional safety concerns were observed with either QVA149 or umeclidinium/vilanterol compared with the monocomponents.

Conclusion

- If combining bronchodilators can optimize bronchodilation and lead to improvements in patient symptoms and morbidity, dual bronchodilators will likely feature prominently in COPD treatment strategies and guidelines in the near future.

Ingelheim, Chiesi, Cytos, Mundipharma, Novartis and Revotar Biopharmaceuticals; and has participated as a speaker in scientific meetings or courses supported by various pharmaceutical companies (Almirall Hermal, AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer and Takeda). In the past 3 years, K-M Beeh has received consulting fees from Ablynx, Apellis Pharmaceuticals, Chiesi and Cytos; and the institution where K-M Beeh is employed (insaf Respiratory Research Institute) has received compensations for the design, performance or participation in single or multicenter clinical trials in the past 3 years from several companies including Almirall, Boehringer Ingelheim, Cytos, GlaxoSmithKline, Mundipharma, Novartis, Pfizer, Revotar Biopharmaceuticals, Sterna AG and TEVA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Global initiative for chronic Obstructive Lung Disease (GOLD 2014). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. www.goldcopd.org/uploads/users/files/GOLD_Report_2014.pdf

•• **GOLD report presents the global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease.**

2 Keating GM. Tiotropium bromide inhalation powder: a review of its use in the management of chronic obstructive pulmonary disease. *Drugs* 72(2), 273–300 (2012).

3 Steiropoulos P, Tzouvelekis A, Bouros D. Formoterol in the management of chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis* 3(2), 205–215 (2008).

4 Stockley RA, Whitehead PJ, Williams MK. Improved outcomes in patients with chronic obstructive pulmonary disease treated with salmeterol compared with placebo/usual therapy: results of a meta-analysis. *Respir. Res.* 7, 147 (2006).

5 Tashkin DP, Littner M, Andrews CP, Tomlinson L, Rinehart M, Denis-Mize K. Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: a placebo-controlled trial. *Respir. Med.* 102(4), 479–487 (2008).

6 Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. *COPD* 6(1), 17–25 (2009).

7 van Noord JA, Aumann JL, Janssens E *et al.* Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur. Respir. J.* 26(2), 214–222 (2005).

8 van Noord JA, Aumann JL, Janssens E *et al.* Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 129(3), 509–517 (2006).

9 Vogelmeier C, Kardos P, Harari S, Gans SJ, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir. Med.* 102(11), 1511–1520 (2008).

10 van Noord JA, Aumann JL, Janssens E *et al.* Combining tiotropium and salmeterol in COPD: effects on airflow obstruction and symptoms. *Respir. Med.* 104(7), 995–1004 (2010).

11 Maltais F, Beck E, Webster D *et al.* Four weeks once daily treatment with tiotropium+olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients. *Eur. Respir. J.* 36(Suppl. 54), Abstract P5557 (2010).

12 Mahler DA, D'Urzo A, Bateman ED *et al.* Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 67(9), 781–788 (2012).

• **Presents results from two 12-week studies which demonstrate the combined efficacy of tiotropium and indacaterol administered concurrently compared with tiotropium alone.**

13 Beeh KM, Beier J. Optimising bronchodilatiation in COPD: double bronchodilator therapy. *Hot Topics Respir. Med.* doi:10.4147/HTR122113 (2012) (Epub ahead of print).

14 COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. The COMBIVENT Inhalation Solution Study Group. *Chest* 112(6), 1514–1521 (1997).

15 COMBIVENT Inhalation Solution Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest* 105(5), 1411–1419 (1994).

16 Johnson M. The beta-adrenoceptor. *Am. J. Respir. Crit. Care Med.* 158(5 Pt 3), S146–S153 (1998).

17 Roux E, Molimard M, Savineau JP, Marthan R. Muscarinic stimulation of airway smooth muscle cells. *Gen. Pharmacol.* 31(3), 349–356 (1998).

18 Barnes PJ. Distribution of receptor targets in the lung. *Proc. Am. Thorac. Soc.* 1(4), 345–351 (2004).

19 Carstairs JR, Nimmo AJ, Barnes PJ. Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. *Am. Rev. Respir. Dis.* 132(3), 541–547 (1985).

20 Mak JC, Barnes PJ. Autoradiographic visualization of muscarinic receptor subtypes in human and guinea pig lung. *Am. Rev. Respir. Dis.* 141(6), 1559–1568 (1990).

21 Postma DS, Keyzer JJ, Koëter GH, Sluiter HJ, De Vries K. Influence of the parasympathetic and sympathetic nervous system on nocturnal bronchial obstruction. *Clin. Sci. (Lond.)* 69(3), 251–258 (1985).

22 Gaultier C, Reinberg A, Girard F. Circadian rhythms in lung resistance and dynamic lung compliance of healthy children. Effects of two bronchodilators. *Respir. Physiol.* 31(2), 169–182 (1977).

23 Furlan R, Guzzetti S, Crivellaro W *et al.* Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation* 81(2), 537–547 (1990).

24 Aizawa H, Inoue H, Ikeda T, Hirose T, Ito Y. Effects of procaterol, a beta-2-adrenoceptor stimulant, on neuroeffector transmission in human bronchial tissue. *Respiration* 58(3–4), 163–166 (1991).

25 Rhoden KJ, Meldrum LA, Barnes PJ. Inhibition of cholinergic neurotransmission in human airways by beta 2-adrenoceptors. *J. Appl. Physiol.* 65(2), 700–705 (1988).

26 Brichetto L, Song P, Crimi E, Rehder K, Brusasco V. Modulation of cholinergic responsiveness through the beta-adrenoceptor signal transmission pathway in bovine trachealis. *J. Appl. Physiol.* 95(2), 735–741 (2003).

27 Novartis. Press Release. Novartis first in class once-daily dual bronchodilator Ultibro® Breezhaler® (QVA149) gains positive CHMP opinion for the treatment of COPD. 26 July 2013. www.novartis.com/newsroom/media-releases/en/2013/1718973.shtml

28 Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. *Int. J. Chron. Obstruct. Pulmon. Dis* 7, 503–513 (2012).

29 D'Urzo A, Ferguson GT, van Noord JA *et al.* Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir. Res.* 12(1), 156 (2011).

30 Kerwin E, Hébert J, Gallagher N *et al.* Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur. Respir. J.* 40(5), 1106–1114 (2012).

31 McKeage K. Indacaterol: a review of its use as maintenance therapy in patients with chronic obstructive pulmonary disease. *Drugs* 72(4), 543–563 (2012).

32 Cazzola M, Bardaro F, Stirpe E. The role of indacaterol for chronic obstructive pulmonary disease (COPD). *J. Thorac. Dis.* 5(4), 559–566 (2013).

33 European Medicines Agency (EMA). Ultibro Breezhaler Summary of Product Characteristics. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002679/WC500151255.pdf

34 GlaxoSmithKline. Press Release. ANORO™ ELLIPTA™ approved as first once-daily dual bronchodilator for the treatment of COPD in the US. www.gsk.com/media/press-releases/2013/anoro_-ellipta_-approved-as-first-once-daily-dual-bronchodilator.html

35 GlaxoSmithKline. Press Release. Anoro® (umeclidinium/vilanterol) receives positive opinion from the CHMP in Europe for the treatment of COPD. www.gsk.com/media/press-releases/2014/anoro---umeclidinium---vilanterol--receives-positive-opinion-fro.html

36 GlaxoSmithKline. Press Release. GSK receives positive CHMP opinion for Incruse® (umeclidinium) for the treatment of COPD. www.gsk.com/media/press-releases/2014/gsk-receives-positive-chmp-opinion-for-incruse---umeclidinium--f.html

37 Decramer M, Maltais F, Feldman G *et al.* Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. *Respir. Physiol. Neurobiol.* 185(2), 393–399 (2013).

38 Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 µg in COPD. *Respir. Med.* 107(10), 1538–1546 (2013).

•• **Study DB2113373 demonstrates that umeclidinium/vilanterol, a combination of long-acting bronchodilators, can provide improvements in lung function compared with the monocomponents umeclidinium and vilanterol.**

39 Trivedi R, Richard N, Mehta R, Church A. Umeclidinium in patients with COPD: a randomised, placebo-controlled study. *Eur. Respir. J.* 43(1), 72–81 (2014).

40 Hanania NA, Feldman G, Zachgo W *et al.* The efficacy and safety of the novel long-acting β_2 agonist vilanterol in patients with COPD: a randomized placebo-controlled trial. *Chest* 142(1), 119–127 (2012).

41 Bateman ED, Ferguson GT, Barnes N *et al.* Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur. Respir. J.* 42(6), 1484–1494 (2013).

•• **SHINE study shows that QVA149, a combination of glycopyrronium and indacaterol, provides improvements in lung function and symptoms compared with the monocomponents and tiotropium.**

42 Vogelmeier CF, Bateman ED, Pallante J *et al.* Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir. Med.* 1(1), 51–60 (2013).

•• **ILLUMINATE study indicates that QVA149 can provide improvements in lung function and patient-reported outcomes versus the long-acting β_2-agonist/inhaled corticosteroid salmeterol/fluticasone propionate.**

43 Beeh K-M, Korn S, Beier J *et al.* Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: the BRIGHT study. *Respir. Med.* 108(4), 584–592 (2014).

44 Dahl R, Chapman KR, Rudolf M *et al.* Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir. Med.* 107(10), 1558–1567 (2013).

45 Wedzicha JA, Decramer M, Ficker JH *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind,

parallel-group study. *Lancet Respir. Med.* 1(3), 199–209 (2013).

•• **SPARK study demonstrates that QVA149 can reduce exacerbations compared with glycopyrronium in patients at risk of exacerbation.**

46 Asai K, Minakata Y, Hirata K *et al.* QVA149 once-daily is safe and well tolerated and improves lung function and health status in Japanese patients with COPD: The ARISE study. *Eur. Respir. J.* 42(Suppl. 57), Abstract P3392 (2013).

47 Mahler DA, Decramer M, D'Urzo A *et al.* Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: BLAZE study. *Eur. Respir. J.* doi:10.1183/090300124013 (2013) (Epub ahead of print).

48 Dahl R, Jadayel D, Alagappan VK, Chen H, Banerji D. Efficacy and safety of QVA149 compared with the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. *Int. J. Chron. Obstruct. Pulmon. Dis.* 8, 501–508 (2013).

49 Celli B, Crater G, Kilbride S *et al.* Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. *Chest* doi:10.1378/chest.13–1579 (2014) (Epub ahead of print).

50 Anzueto A, Decramer M, Kaelin T, Richard N, Tabberer M, Harris S, Church A. The efficacy and safety of umeclidinium/vilanterol compared with tiotropium or vilanterol over 24 weeks in subjects with COPD. Presented at: *109th American Thoracic Society International Conference.* PA, USA, 17–22 May 2013 (Poster 42837).

51 Decramer M, Anzueto A, Kerwin E, Richard N, Crater G, Tabberer M, Harris S, Church A. Efficacy and safety of umeclidinium/vilanterol compared with umeclidinium or tiotropium in COPD. Presented at: *23rd European Respiratory Society Annual Cogress.* Barcelona, Spain, 7–11 September 2013 (Poster P3640).

52 Maltais F, Singh S, Donald A, Church A, Crater G, Goh A, Riley J. Effects of a combination of vilanterol and umeclidinium on exercise endurance in subjects with COPD: two randomised clinical trials. Presented at: *23rd European Respiratory Society Annual Congress.* Barcelona, Spain, 7–11 September 2013 (Poster P761).

53 Donohue J, Niewoehner D, Brooks J, O'Dell D, Church A. Long-term safety and tolerability of umeclidinium/vilanterol and umeclidinium in COPD. Presented at: *23rd European Respiratory Society Annual Congress.* Barcelona, Spain, 7–11 September 2013 (Poster 760).

54 GlaxoSmithKline Clinical Study Register. Result summary DB2116133. A randomized, double-blind, 3-way, cross-over study to evaluate lung function response after treatment with umeclidinium 62.5 µg, vilanterol 25 µg, and umeclidinium/vilanterol 62.5/25 µg once-daily in subjects with chronic obstructive pulmonary disease (COPD). www.gsk-clinicalstudyregister.com/files2/a4eb7507-0808-4196-b85d-70c63e287917

55 Clinicaltrials.gov. NCT01777334 (ZEP117115). The purpose of this study is to evaluate the spirometric effect (Trough FEV_1) of umeclidinium/vilanterol 62.5/25 µg once daily compared with tiotropium 18 µg once daily over a 24-week treatment period in subjects with COPD. http://clinicaltrials.gov/ct2/show/NCT01777334?term=NCT01777334&rank=1

56 FDA. Briefing Document. Pulmonary-Allergy Drugs Advisory Committee Meeting. NDA 203–975: umeclidinium and vilanterol inhalation powder for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm367411.pdf

57 GlaxoSmithKline. FDA Advisory Committee Briefing Document. ANORO™ ELLIPTA™ (umeclidinium bromide/vilanterol inhalation powder) for treatment of chronic obstructive pulmonary disease. NDA 203975. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM367414.pdf

58 Witek TJ, Jr., Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur. Respir. J.* 21(2), 267–272 (2003).

59 GlaxoSmithKline Clinical Study Register. Result summary DB2116844. Results report for a meta-analysis of DB2113360 and DB2113374: an integrated review of transitional dyspnoea index data for umeclidinium/vilanterol, umeclidinium, vilanterol and tiotropium over 24 weeks in subjects with COPD. www.gsk-clinicalstudyregister.com/files2/1f37e00a-6090–4648–9a79–4e49e481af40

60 Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2(1), 75–79 (2005).

61 Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 300(12), 1439–1450 (2008).

62 Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. *Int. J. Chron. Obstruct. Pulmon. Dis.* 3(1), 163–169 (2008).

63 Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease systematic review and meta-analysis of randomised controlled trials. *BMJ* 342, d3215 (2011).

64 Wise RA, Anzueto A, Cotton D *et al.* Tiotropium Respimat inhaler and the risk of death in COPD. *N. Engl. J Med* 369(16), 1491–1501 (2013).

65 Vogelmeier C, Verkindre C, Cheung D *et al.* Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Pulm. Pharmacol. Ther.* 23(5), 438–444 (2010).

66 Worth H, Chung KF, Felser JM, Hu H, Rueegg P. Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Respir. Med.* 105(4), 571–579 (2011).

67 Beier J, Chanez P, Martinot JB *et al.* Safety, tolerability and efficacy of indacaterol, a novel once-daily β_2-agonist, in patients with COPD: a 28-day randomised, placebo

controlled clinical trial. *Pulm. Pharmacol. Ther.* 20(6), 740–749 (2007).

68 Chapman KR, Beeh KM, Beier J *et al.* A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. *BMC Pulm. Med.* 14(1), 4 (2014).

69 Feldman G, Siler T, Prasad N *et al.* Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomised, 12-week study. *BMC Pulm. Med.* 10, 11 (2010).

70 Donohue JF, Fogarty C, Lötvall J *et al.* Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am. J. Respir. Crit. Care Med.* 182(2), 155–162 (2010).

71 Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B. Long-term safety and efficacy of indacaterol, a long-acting β_2-agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest* 140(1), 68–75 (2011).

72 Kornmann O, Dahl R, Centanni S *et al.* Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur. Respir. J.* 37(2), 273–279 (2011).

73 Dahl R, Chung KF, Buhl R *et al.* Efficacy of a new once-daily long-acting inhaled β_2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 65(6), 473–479 (2010).

74 Welte T, Vogelmeier C, Dahl R *et al.* Once-daily QVA149 has a good safety profile in patients with COPD. *Eur. Respir. J.* 42 (Suppl. 57), 143s–144s (2013) Presented at: *The 23rd European Respiratory Society Annual Congress*. Barcelona, Spain, 7–11 September 2013 (Poster P757).

75 Ferguson GT, Barnes N, Mehta R, D'Andrea P, Chen H, Banerji D. Cardio- and cerebro-vascular safety of QVA149: results from a pooled analysis. *Eur. Respir. J.* 42(Suppl. 57), Abstract P4139 (2013).

76 Clinicaltrials.gov. NCT01610037 (RADIATE; A2339). Comparison of long-term safety of the combination product QVA149A against placebo and standard of care treatment in chronic obstructive pulmonary disease patients with moderate to severe airflow limitation. http://clinicaltrials.gov/ct2/show/NCT01610037?term=01610037&rank=1

77 Clinicaltrials.gov. NCT01782326 (FLAME; A2318). QVA vs. salmeterol/fluticasone, 52-week exacerbation study. http://clinicaltrials.gov/ct2/show/NCT01782326?term=01782326&rank=1

78 Clinicaltrials.gov. NCT01709903 (LANTERN; A2331). A 26-week treatment randomized, double-blind, double dummy, parallel-group study to assess the efficacy, safety and tolerability of QVA149 (indacaterol / glycopyrronium bromide) compared with fluticasone/salmeterol in patients with moderate to severe chronic obstructive pulmonary disease. http://clinicaltrials.gov/ct2/show/NCT01709903?term=NCT01709903&rank=1

79 Clinicaltrials.gov. NCT01899742 (DB2116960). The purpose of this study is to evaluate the spirometric effect (trough FEV_1) of umeclidinium/vilanterol 62.5/25 µg once daily compared with tiotropium 18 µg once daily over a 12-week treatment period in subjects with COPD who continue to have symptoms on tiotropium. http://clinicaltrials.gov/ct2/show/NCT01899742?term=NCT01899742&rank=1

80 Clinicaltrials.gov. NCT01817764 (DB2114930). A study to compare the efficacy and safety of umeclidinium/vilanterol and fluticasone propionate/salmeterol in subjects with chronic obstructive pulmonary disease (COPD). http://clinicaltrials.gov/ct2/show/NCT01817764?term=NCT01817764&rank=1

81 Clinicaltrials.gov. NCT01879410 (DB2114951). A study to compare the efficacy and safety of umeclidinium/vilanterol and fluticasone propionate/salmeterol in subjects with chronic obstructive pulmonary disease (COPD). http://clinicaltrials.gov/ct2/show/NCT01879410?term=NCT01879410&rank=1

82 Clinicaltrials.gov. NCT01822899 (DB2116134). A study to evaluate the efficacy and safety of umeclidinium bromide/vilanterol compared with fluticasone propionate/salmeterol over 12 weeks in subjects with chronic obstructive pulmonary disease (COPD). http://clinicaltrials.gov/ct2/show/NCT01822899?term=NCT01822899&rank=1

83 Toy EL, Beaulieu NU, McHale JM *et al.* Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respir. Med.* 105(3), 435–441 (2011).

84 Yu AP, Guérin A, Ponce de Leon D *et al.* Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. *J. Med. Econ.* 14(4), 486–496 (2011).

85 Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am. J. Respir. Crit. Care Med.* 189(3), 250–255 (2014).

- **Paper discusses the strengths and limitations of using minimum clinically important differences in pharmacological trials.**

86 Westwood M, Bourbeau J, Jones PW, Cerulli A, Capkun-Niggli G, Worthy G. Relationship between FEV_1 change and patient-reported outcomes in randomised trials of inhaled bronchodilators for stable COPD: a systematic review. *Respir. Res.* 12, 40 (2011).

87 Jones PW, Donohue JF, Nedelman J, Pascoe S, Pinault G, Lassen C. Correlating changes in lung function with patient outcomes in chronic obstructive pulmonary disease: a pooled analysis. *Respir. Res.* 12, 161 (2011).

88 Parshall MB, Schwartzstein RM, Adams L *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am. J. Respir. Crit. Care Med.* 185(4), 435–452 (2012).

89 Price D, Hutton C, Stewart R, West D. COPD patients remain symptomatic despite current treatment: a UK primary-care setting analysis. *Prim. Care Respir. J.* 22(4), Abstract 27 (2013).

90 Suissa S, Ernst P, Vandemheen KL, Aaron SD. Methodological issues in therapeutic trials of COPD. *Eur. Respir. J.* 31(5), 927–933 (2008).

91 Barnes PJ. Inhaled corticosteroids in COPD: a controversy. *Respiration* 80(2), 89–95 (2010).

92 Crim C, Calverley PM, Anderson JA *et al.* Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur. Respir. J.* 34(3), 641–647 (2009).

93 Yawn BP, Li Y, Tian H, Zhang J, Arcona S, Kahler KH. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. *Int. J. Chron. Obstruct. Pulmon. Dis.* 8, 295–304 (2013).

94 Vogelmeier C, Bateman ED, Chen H, Banerji D. Comparison of COPD exacerbations with once-daily QVA149 versus twice-daily salmeterol/fluticasone combination: the ILLUMINATE study. *Thorax* 68(Suppl. 3), A184–A185 (Abstract P237) (2013).

95 Cazzola M, Molimard M. The scientific rationale for combining long-acting β_2-agonists and muscarinic antagonists in COPD. *Pulm. Pharmacol. Ther.* 23(4), 257–267 (2010).

96 Canning BJ, Fischer A. Neural regulation of airway smooth muscle tone. *Respir. Physiol.* 125(1–2), 113–127 (2001).

97 Barnes NC, Hashimoto S, Nagase T *et al.* QVA149 provides superior peak lung function in patients with COPD. *Eur. Respir. J.* 42(Suppl. 57), 749s (2013).

98 Bateman ED, Ferguson GT, Welte T *et al.* Dual bronchodilation with once-daily QVA149 significantly improves lung function versus single bronchodilators and salmeterol/fluticasone. *Am. J. Respir. Crit. Care Med.* 187(1), A4271 (2013).

99 Frampton JE. QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease. *Drugs* 74(4), 465–488 (2014).

100 Banerji D, Alagappan V, Green Y *et al.* Dual bronchodilation with once-daily QVA149 improves dyspnea and health status and reduces symptoms and rescue medication use in patients with COPD: the IGNITE trials. *Eur. Respir. J.* 42(Suppl. 57), 693s (2013).