

# NEW OPTIONS FOR OPTIMAL BRONCHODILATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

\*Caroline Charles

*Scilink Medical Writing*

*\*Correspondence to [scilink.mw@gmail.com](mailto:scilink.mw@gmail.com)*

**Disclosure:** Medical writing assistance was funded by Novartis.

**Received:** 15.09.14 **Accepted:** 08.10.14

**Citation:** EMJ Respir. 2014;2:58-66.

---

## ABSTRACT

The European Respiratory Society (ERS) International Congress was held in Munich, Germany, on 6<sup>th</sup>-10<sup>th</sup> September 2014, and was a particularly important opportunity for leading experts to share recent developments and new clinical evidence for the management of chronic obstructive pulmonary disease (COPD). In recent years, new emerging therapies have allowed patients to benefit from improved clinical outcomes and quality of life, with acceptable toxicities. The 2014 guidelines of the Global Initiative for Chronic Obstructive Lung Disease identified symptom reduction as the main goal of moderate-to-severe COPD management. Combined bronchodilation therapy with different therapeutic classes was recommended as a strategy to ensure improved symptom control while containing adverse events, as opposed to monotherapy. Moreover, combination inhaled bronchodilators that are administered once-daily can improve compliance, compared to twice-daily modalities. This review will summarise newly presented clinical data at ERS 2014, providing further information on the efficacy and safety of such combinations, clinical evidence regarding COPD presentation in various populations, strategies for optimal drug delivery, and safety profile monitoring for recent therapeutic options.

**Keywords:** Chronic obstructive pulmonary disease (COPD), QVA149, indacaterol maleate, glycopyrronium bromide, congress highlights.

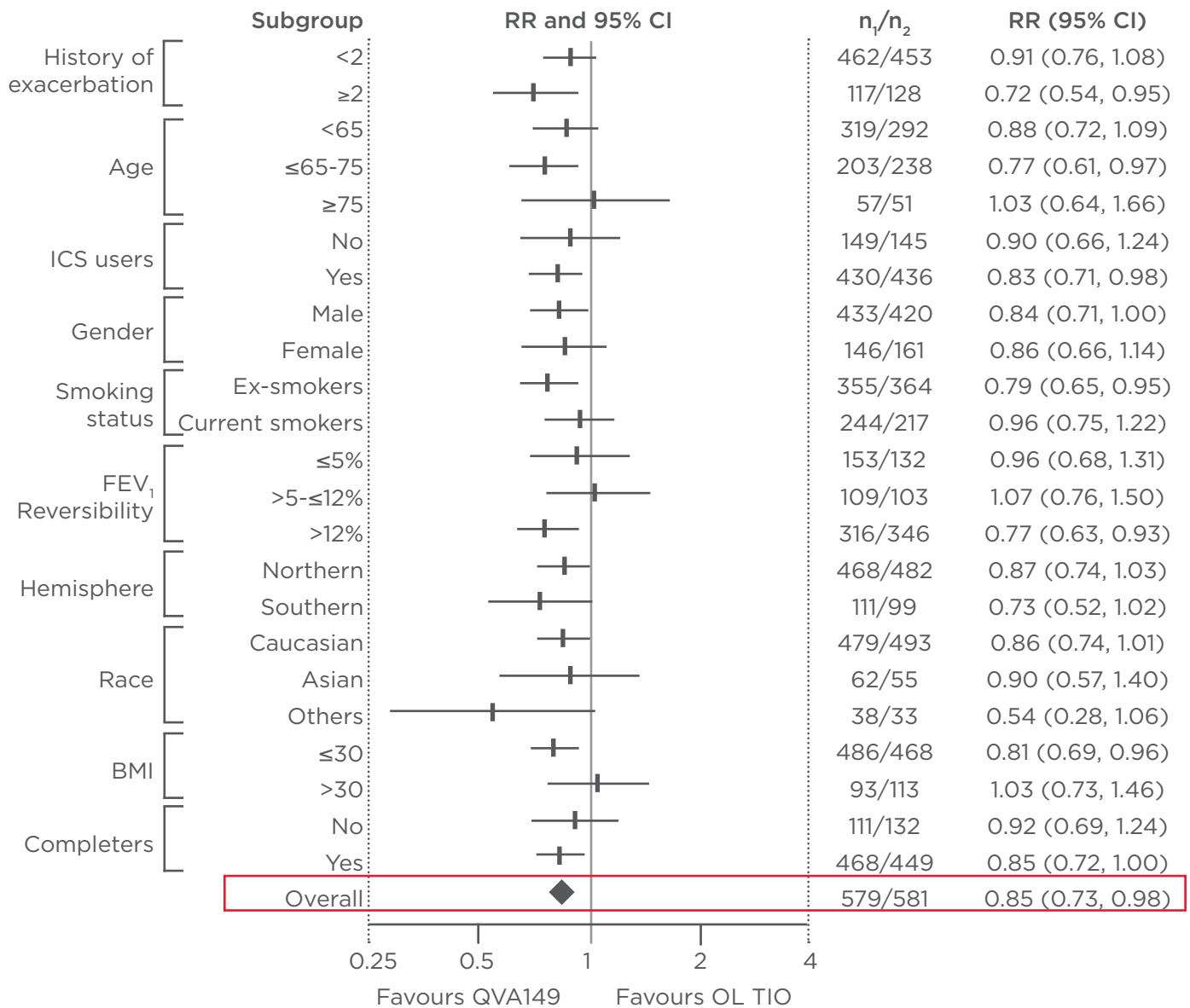
---

## INTRODUCTION

The European Respiratory Society (ERS) International Congress was held in Munich, Germany, on 6<sup>th</sup>-10<sup>th</sup> September 2014, and was a particularly important opportunity for leading experts to share recent developments and new clinical evidence for the management of chronic obstructive pulmonary disease (COPD). COPD, a chronic and potentially life-threatening disease, affects more than 210 million people worldwide<sup>1</sup> and is characterised by progressive reduction in lung function, resulting in dyspnoea and significant impairment of quality of life (QoL).<sup>1-4</sup> Dyspnoea is the main symptom prompting patients to seek treatment, while the prevention of exacerbations is one of the most crucial objectives of COPD management.<sup>5,6</sup> As a result, both parameters are key objectives of newly-developed drugs and were the main endpoints of newly published clinical trial

results, presented at ERS 2014, that demonstrated substantial improvements.

The 2014 guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>7</sup> identified symptom reduction as the main goal of moderate-to-severe COPD management. Combined bronchodilation therapy with different therapeutic classes was recommended as a strategy to ensure improved symptom control while containing adverse events (AEs), as opposed to monotherapy. Long-acting bronchodilators are crucial to COPD management and can provide patients with improved and sustained lung function. This review will summarise newly presented clinical data at ERS 2014, providing further information on the efficacy and safety of such combinations, clinical evidence regarding COPD presentation in various populations, strategies for optimal drug delivery, and safety profile monitoring for recent therapeutic options.



**Figure 1: Overall rate ratio favours QVA149 when compared to open-label tiotropium in the majority of subgroups.**

BMI: body mass index; CI: confidence interval; FEV<sub>1</sub>: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; n<sub>1</sub>/n<sub>2</sub>: number of patients in QVA149 arm/number of patients in OL tiotropium arm; OL: open-label; TIO: tiotropium; RR: rate ratio.

*Adapted from Wedzicha JA et al.<sup>9</sup>*

## NEW CLINICAL EVIDENCE ON QVA149 (INDACATEROL MALEATE/ GLYCOPYRRONIUM BROMIDE)

QVA149 (Ultibro®, Novartis, Basel, Switzerland) is a once-daily (OD) long-acting inhaled bronchodilator used within the low resistance Breezhaler® device, and comprises the combination of indacaterol maleate (IND, a long-acting β<sub>2</sub>-agonist [LABA]) and glycopyrronium bromide (GLY, a long-acting muscarinic antagonist [LAMA]) It is

already approved in over 30 countries for COPD maintenance therapy.

### New Clinical Data on the Risk of COPD Exacerbations

#### The LANTERN study

In the 26-week, multicentre, randomised, double-blind, double-dummy, parallel-group Phase III LANTERN study,<sup>8</sup> QVA149 was evaluated against salmeterol (SAL)/fluticasone (FLU) in terms of

improvement in lung function, dyspnoea, health status, and exacerbations in patients (n=744) with moderate-to-severe COPD (with a history of zero or one exacerbation in the last 12 months). QVA149 met the primary endpoint of lung function non-inferiority to SAL/FLU, followed by statistically significant superiority in post-dose trough forced expiratory volume in 1 second (FEV<sub>1</sub>) after 26 weeks of treatment (p<0.001). Moreover, QVA149 demonstrated superiority with respect to the annualised rate of moderate-to-severe exacerbations with a 31% reduction, as compared to SAL/FLU (p=0.048).

### The SPARK study

The SPARK study<sup>9</sup> was a 64-week multicentre, randomised, double-blind, active-control, parallel-group study that aimed to evaluate the efficacy and safety of QVA149 treatment on COPD exacerbations, versus GLY and tiotropium (TIO). Patients (n=2,224) with severe or very severe COPD (GOLD Stage 3 or 4) were randomly (1:1:1) assigned to QVA149 110/50 µg, GLY 50 µg, or TIO 18 µg. Earlier results, as published by Wedzicha et al.,<sup>2</sup> established superiority of QVA149 over GLY, with a 12% reduction of the annualised rate of moderate-to-severe exacerbations versus GLY (p=0.038); the safety profiles for the three treatment arms were comparable. In a post-hoc analysis presented by Wedzicha et al.,<sup>9</sup> the rate ratio of exacerbations in severe COPD patients was analysed. The risk of moderate-to-severe exacerbation was 11% and 15% lower with QVA149, as compared with GLY (rate ratio, 0.89; 95% CI, 0.77, 1.04) and TIO (rate ratio, 0.85; 95% CI, 0.73, 0.98), respectively. Similar results were obtained across a majority of subgroups (Figure 1). No significant differences in safety profiles were observed across the three treatment arms.

## New Clinical Data on Lung Function/Dyspnoea Management

### The QUANTIFY Study

The QUANTIFY study<sup>10</sup> was a double-blind, triple-dummy study which aimed to compare the clinical outcomes of QVA149 treatment with a free-dose combination of TIO + formoterol (FOR) in patients with moderate-to-severe COPD, as evaluated by health-related QoL (St. George's Respiratory Questionnaire-COPD [(SGRQ)-C]), lung function (FEV<sub>1</sub>, forced vital capacity [FVC]), and dyspnoea (transition dyspnoea index [TDI] responder rate).

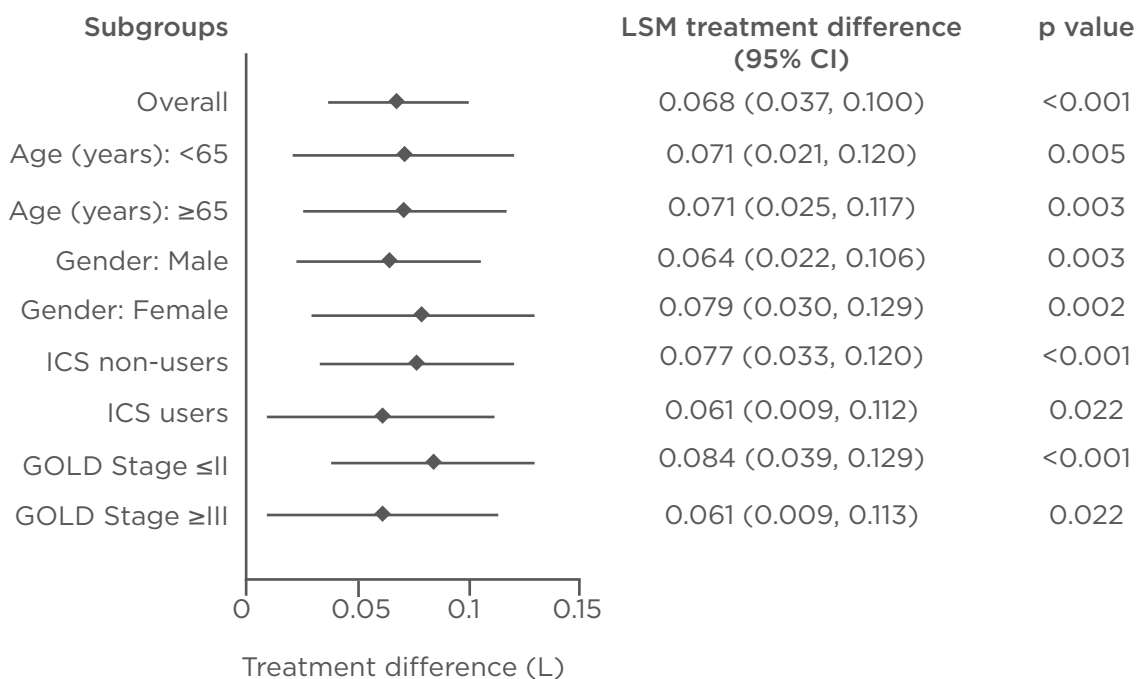
Patients (n=934) were 1:1 randomised to either QVA149 110/50 µg OD or TIO 18µg OD + FOR 12µg twice-daily. At 26 weeks, QVA149 demonstrated statistically significant improvements in lung function (FEV<sub>1</sub> and FVC p<0.001 and p<0.001, respectively; Figure 2), significant improvements in dyspnoea (p<0.05), and non-inferiority in terms of QoL over the standard-of-care combination of TIO+FOR. No differences in safety profiles were observed between both treatment arms.

### The BLAZE study

The BLAZE study<sup>11</sup> was a multicentre, randomised, blinded, double-dummy, placebo-controlled, three-period crossover study which evaluated the clinical outcomes and safety of QVA149 versus TIO and placebo in moderate-to-severe COPD. Study design included six treatment sequences comprising three active treatment phases (QVA, TIO, or placebo) for 42 days, separated by 14-day washout phases. All the patients (n=247) received the three treatment options, but with different sequential orders. Previously published results demonstrated significant improvements with QVA149 regarding dyspnoea, lung function, and reduced rescue medication over TIO and placebo, as early as 6 weeks into therapy.<sup>12</sup> D'Urzo et al.<sup>11</sup> reported the outcomes for a subpopulation of patients (n=82) who received LABA and inhaled corticosteroids (ICS) prior to the study, which is highly interesting because this therapeutic strategy is not recommended by current 2014 GOLD guidelines.<sup>7</sup>

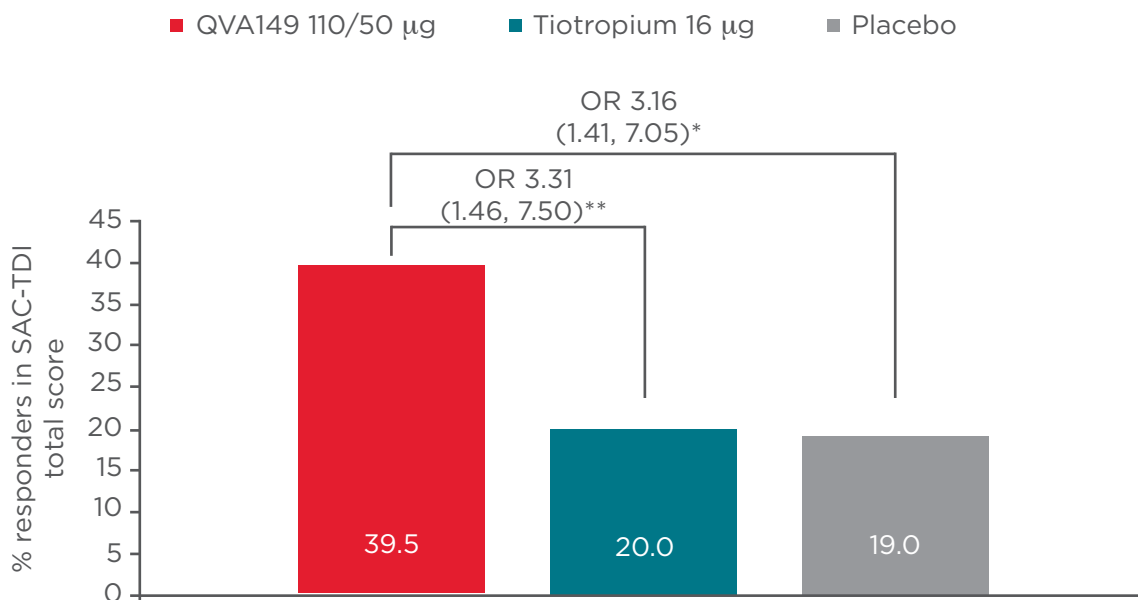
At 6 weeks, QVA significantly improved dyspnoea in a greater proportion of patients compared to TIO and placebo (p<0.05 for both comparisons), as evaluated by the proportion of patients achieving minimum clinically important difference (an assessment used to identify responders in clinical trials)<sup>13</sup> in self-administered computerised-total dyspnoea index (SAC-TDI) total score (Figure 3). Similar outcomes were observed in terms of rapid and sustained bronchodilation at day 1 and after 6 weeks, with statistically significant improvements in lung function (FEV<sub>1</sub>). Rescue medication use was significantly reduced with QVA149 compared to placebo (QVA149 versus TIO, not significant). Safety parameters and AE occurrences as evaluated between QVA149 and TIO were similar, and the treatments were well tolerated. Similarly, a post-hoc subgroup analysis from the same study was also presented at ERS 2014, and focused on patients receiving LAMA as prior medication.<sup>14</sup> QVA149 was also associated,

versus placebo or TIO, with significantly improved  $p < 0.001$ , and reduction of rescue medication dyspnoea (SAC-TDI,  $p < 0.001$ ), lung function ( $FEV_1$ , (daily puffs  $p < 0.01$ ).



**Figure 2: Forest plot of pre-dose  $FEV_1$  at Week 26 (LOCF) by subgroups (QVA149 versus TIO+FOR).** ICS: inhaled corticosteroids; LOCF: last observation carried forward; LSM: least squares mean; TIO+FOR: tiotropium plus formoterol.

Adapted from Gessner C et al.<sup>10</sup>



**Figure 3: Percentage of responders in SAC-TDI total score in patients using prior LABA/ICS medication after 6 weeks of treatment.**

\* $p = 0.005$ ; \*\* $p = 0.004$

SAC-TDI: self-administered computerised version of transition dyspnoea index; LABA: long-acting  $\beta_2$ -agonist; ICS: inhaled corticosteroids; OR: odds ratio.

Adapted from D'Urzo A et al.<sup>11</sup>

## New Preclinical Data on Drug Delivery with the Breezhaler® Device

For many inhalation devices, establishing the dose-response relationship for consistent and reliable lung delivery is hindered by inter-individual variability, physiological and inspiration parameters, lack of reliable correlation between plasma levels, and efficacy quantification, as well as the small statistical power of available measurements and methods. The Breezhaler® device is a low-resistance device that can provide optimal drug deposition and reliable dose control, which is of importance as patient-related factors such as poor handling and inhalation technique may result in suboptimal drug delivery to the lower airway.<sup>15-17</sup>

As such, Kuttler et al.<sup>18</sup> reported the results of a drug-delivery modelisation study on the Breezhaler® device, aiming to determine optimal lung deposition parameters for QVA149 among variable simulated flow rates, and particle sizes in a mouth-throat model. Measurements in flow profile and turbulences aimed to evaluate the regions for greater drug loss according to the variable parameters. The results demonstrated a correlation between particle size and deposition in bronchial tissue, as well as an increased loss of drug in the mouth-throat region at a high flow rate, and a greater drug loss in the capsule/device at lower flow rates, suggesting a constant delivery of QVA149 to lung tissue across the flow rates via the Breezhaler® device. Moreover, higher drug losses were observed when GLY or IND were administered as monotherapy through the same device, in comparison with QVA149, indicating improved and optimised delivery with the fixed-dose combination.

### NEW CLINICAL EVIDENCE ON GLY

GLY (Seebri®, Novartis) is an already approved OD LAMA used within the low-resistance Breezhaler® device for COPD maintenance therapy.

## New Clinical Data on Lung Function/Dyspnoea Management: the GLOW6 study

As stated above, current GOLD guidelines<sup>7</sup> recommend the combination of different therapeutic classes (LABAs, LAMAs, and ICS) in dual or triple therapy to ensure optimal management of COPD patients and improved clinical outcomes with similar safety profiles, as compared with monotherapy. Nevertheless, to date, clinical data

on triple combination strategies remain scarce.<sup>19</sup> The GLOW6 study<sup>20</sup> was a 12-week, multicentre, randomised, double-blind, parallel-group, placebo-controlled study aiming to compare the efficacy and safety of GLY+IND combination therapy versus IND monotherapy in moderate-to-severe patients (n=449), and for which the results were previously published.<sup>21</sup> In a post-hoc analysis (n=280), Vincken et al.<sup>21</sup> presented the efficacy and safety results of free-dose triple combination (GLY + IND + ICS) versus free-dose double combination (IND + ICS) therapy. The triple combination yielded significantly higher improvements in lung function (as assessed by FEV<sub>1</sub>, as early as day 1, p=0.012) and dyspnoea at 12 weeks (p=0.041) versus the double combination. The safety profiles of both regimens were comparable with no clinically meaningful differences.

## New Clinical Data on Lung Function and Health Status: the GLISTEN study

Frith et al.<sup>22</sup> presented the results of the GLISTEN study, a multicentre, randomised, blinded, double-dummy placebo and active-controlled, 3-arm parallel group, 12-week trial aiming to assess non-inferiority of inpatients with COPD already receiving the ICS/LABA FLU/SAL. The study met its primary endpoint as the GLY combination with FLU/SAL demonstrated non-inferiority to TIO+FLU/SAL in terms of trough FEV<sub>1</sub> at 12 weeks. The former combination also demonstrated superiority over FLU/SAL alone, as demonstrated by statistically and clinically significant improvements in trough FEV<sub>1</sub> at week 12 (p<0.001). Overall, the safety profile of all three arms was acceptable and consistent among treatment subgroups.

## Post-marketing Surveillance Data

In an innovative analysis of post-market surveillance reports with the EMPIRICA™ Signal System (Oracle Health Sciences) data mining tool, Di Giovanni et al.<sup>23</sup> evaluated the safety profile of GLY since its launch in September 2012 through to March 2014. The EMPIRICA tool was used to detect and calculate any disproportionate statistic for AEs, using the multi-item Gamma Poisson Shrinker algorithm. In parallel, a traditional approach was used in the form of evaluation of individual case safety reports, scientific literature, spontaneous reports, competent authorities, non-interventional studies, and compassionate use programmes. The analyses through both approaches



revealed a consistent safety profile with regards to the approved label, particularly with regards to cardiovascular AEs and serious AEs. No new safety hazard was detected.

## NEW CLINICAL EVIDENCE ON TIO + OLODATEROL COMBINATION

Data from the TONADO studies - two 52-week, double-blind, parallel-group studies - were presented at ERS 2014, and evaluated the efficacy and safety of the combination of TIO + olodaterol (a LABA) in a single inhaler (Respimat® Inhaler, Boehringer Ingelheim) versus TIO or olodaterol alone in 5,162 patients with COPD.<sup>24</sup> At 24 weeks, the combination was superior ( $p < 0.001$ ) to monotherapy with either TIO or olodaterol in terms of lung function (trough FEV<sub>1</sub> response) and QoL (SGRQ), these improvements being clinically relevant.<sup>24</sup> Overall, the safety profile of the combination was consistent with those of TIO or olodaterol therapy alone.<sup>25</sup>

## DEFINING AND IDENTIFYING NEW STRATEGIES

### Stepwise Withdrawal of ICS and Lung Function

The WISDOM study,<sup>26-28</sup> a 12-month, double-blind, parallel-group, active-controlled study, aimed to evaluate the impact of stepwise withdrawal of ICS on lung function in GOLD 3/4 COPD patients ( $n = 2,485$ ) receiving the combination of TIO, SAL, and FLU. After 6 weeks, patients were randomised to either continue therapy or to undergo stepwise withdrawal of ICS over 12 weeks (dose reduction every 6 weeks). ICS withdrawal was non-inferior to ICS use in lung function, as assessed by trough FEV<sub>1</sub>, at both 18 and 52 weeks ( $p > 0.0001$  and  $p < 0.01$ , respectively) and in the risk of moderate-to-severe exacerbations. The authors explained that these results demonstrated that many patients with severe COPD may not require ICS use, despite the latter being recommended by GOLD guidelines, which is interesting in clinical practice because ICS represent a potential for an additional burden due to their related AEs.

### New Clinical Evidence on Blood Eosinophil Levels and the Risk of COPD Exacerbations

Two studies explored the utility of measuring blood eosinophil levels with respect to the risk of COPD exacerbation in patients receiving ICS therapy. The findings resulted from post-hoc analyses

conducted on trials evaluating Relvar® Ellipta® (GlaxoSmithKline, FLU + vilanterol, a LABA) and Anoro® Ellipta® (GlaxoSmithKline, umeclidinium [a LAMA] + vilanterol [a LABA] OD combination). The results revealed that baseline blood eosinophil count could be a biomarker of improvement of exacerbation rates in patients receiving FLU + vilanterol, the higher the eosinophil level, the greater the improvement.<sup>29</sup> However, a post-hoc analysis on patients who received umeclidinium and vilanterol, either as monotherapy or in combination, did not reveal any differences in terms of responsiveness to bronchodilator treatment according to the blood eosinophil count, meaning that this measurement is not a predictor of response to bronchodilator treatment.<sup>30</sup>

## REAL-LIFE DATA ON COPD

Over recent years, several initiatives have emerged to implement registries and studies in order to collect real-life data on COPD presentation in the general population, as well as treatment pathways and prescription behaviours. Indeed, obtaining data reflective of real-world populations as opposed to clinical trial populations is very important to help refine management guidelines and identify patients likely to respond better to select therapies.

### COPD Distribution and Disease Characteristics in a German population

The DACCORD study<sup>31</sup> was a national, prospective observational cohort study initiated in Germany across 349 centres, collecting data from 6,208 patients with COPD, with an enrolment based on GLY medication (2:1). The main objective was to evaluate the distribution of COPD patients among all four GOLD 2011 categories (ABCD groups, assessing both lung function and symptoms and risks of experiencing exacerbations).<sup>32</sup> A wide range of clinical and therapeutic parameters were recorded, including spirometry, history of exacerbations, COPD assessment test (CAT), Modified Medical Research Council Dyspnoea Scale, comorbidities, smoking history, and long-term oxygen use.

Preliminary results revealed that the majority of patients had mild (17.8%) to moderate (48.5%) disease (GOLD 2010 criteria),<sup>33</sup> with 50.4% of patients being classified in C and D categories (GOLD 2011 criteria)<sup>32</sup> according to lung function and exacerbation history. In the 6-month period prior to enrolment, 27.6% of patients experienced

COPD exacerbations, with 7.8% of patients suffering from two or more episodes.<sup>34</sup> Higher CAT score (>30) was associated with a high exacerbation frequency (48.6%), as compared with CAT score <10 (16.2%). However, no significant differences were observed regarding GLY use or age distribution. The study will span over the next 2 years, interim 1-year data being expected by early 2015.

### Treatment Pathways and Prescription Patterns within a UK Population

In a global, retrospective, observational study, the prescribing patterns 1 year prior, and up to 13 years following, initial diagnosis of COPD were recorded in order to identify the main treatment pathways from diagnosis to triple therapy, predictors for prescription, and the rationale behind the choice of initial therapy.<sup>35,36</sup> The UK patient dataset results were presented at ERS, and included data from 20,154 patients from 318 practices, using the Optimum Patient Care Research Database

which collects anonymous longitudinal data from >1 million UK patients. In the first analysis subset,<sup>35</sup> data from the 16,185 patients composing the final study population revealed that the main predictors for prescription of first therapy and first maintenance therapy for COPD were comorbid asthma, increasing exacerbation rates, and decreasing lung function.

After excluding patients with comorbid asthma, the analysis revealed that the prescribing patterns were not consistent with GOLD first and second choice recommended therapies according to GOLD category. Long-acting bronchodilator monotherapies were underused, particularly in GOLD A and B categories in which ICS regimens were prescribed (33 and 36% of patients, respectively), despite not being recommended. Overall, ICS monotherapy was prescribed across all four GOLD categories, despite also not being recommended (Figure 4).

Initial therapy	GOLD group, n (%)				Total n (%)
	A	B	C	D	
None	1,784 (34)	982 (31)	597 (27)	590 (26)	3,953 (31)
Short-acting agents	1,506 (29)	927 (29)	575 (26)	520 (23)	3,528 (27)
LABA	51 (1)	61 (2)	32 (1)	49 (2)	193 (2)
LAMA	149 (3)	67 (2)	76 (3)	56 (3)	348 (3)
LABA + LAMA	7 (0.1)	2 (0.1)	3 (0.1)	8 (0.4)	20 (0.2)
ICS	831 (16)	551 (17)	362 (16)	395 (17)	2,139 (17)
ICS + LABA	746 (14)	503 (16)	487 (22)	538 (24)	2,274 (18)
ICS + LAMA	43 (1)	22 (1)	27 (1)	19 (1)	111 (1)
ICS + LABA + LAMA	93 (2)	71 (2)	88 (4)	89 (4)	341 (3)
Other	4 (0.1)	5 (0.2)	0 (0)	6 (0.3)	15 (0.1)
<b>Total n (%)</b>	<b>5,214 (100)</b>	<b>3,191 (100)</b>	<b>2,247 (100)</b>	<b>2,270 (100)</b>	<b>12,922 (100)</b>
First choice therapy	29%	4%	23%	42%	
First or second choice therapy	33%	4%	23%	43%	
Not on recommended therapy by GOLD 2013	67%	96%	77%	58%	

■ GOLD first choice therapy ■ GOLD second choice therapy

**Figure 4: Initial therapy by GOLD Group for non-asthma patients only.**

LABA: long-acting  $\beta_2$ -agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Adapted from Price D et al.<sup>35</sup>

In another subset,<sup>36</sup> the results from 11,858 patients without comorbid asthma showed that about 29% of patients received triple combination therapy after initial diagnosis. The majority of patients who progressed to triple combination therapy did so within 3 years of initial diagnosis; the GOLD category did not have an impact to progression to triple therapy.

### Disease, Patients, and Treatment-Related Parameters in an Italian Population

The methodology<sup>37</sup> and preliminary results<sup>38</sup> of the 3-year MISTRAL study - an Italian, observational, longitudinal, prospective multicentre trial - were presented at ERS 2014. The aim of this study was to describe the therapeutic approaches and COPD management evolution as defined by the GOLD guidelines, in both patients with frequent and non-frequent exacerbations.<sup>32</sup> Indeed, the identification of patients more likely to respond to therapy is a crucial objective and recent findings indicate that adherence to GOLD guidelines is low,<sup>39</sup> warranting a large-scale, real-life study tailored to acquire treatment pathway prescription trends and prognostic factors and parameters.

With an enrolment target of 1,500 patients within 72 centres, this study involves 1 enrolment visit and 6 follow-up visits every 6 months. Patient characteristics, clinical outcomes, patient-

related parameters, and treatment-related parameters were documented. Preliminary results were presented on the female subpopulation, which is of particular interest as recent reports suggest that women could be at higher risk of COPD and may present more invalidating symptoms and COPD exacerbations than men.<sup>40-43</sup> Between the two cohorts, women represented 21-24% of the subjects (men/women ratio, 3.5:1). Data from the first 139 women suggested that this subpopulation is younger, with a younger age at diagnosis, and presents shorter disease duration. However, a comparison of the female versus male cohorts revealed that a higher percentage of women were smoking at the time of the study.

### CONCLUSION

In recent years, new emerging therapies have achieved improved clinical outcomes and QoL with acceptable toxicities. Combination inhaled bronchodilators that are administered OD can improve compliance compared to twice-daily modalities. Nevertheless, some unmet needs are yet to be addressed, and COPD remains a disease associated with a high burden. Registries and observational studies will certainly help to identify patient subsets most likely to benefit from select therapies, as well as help to refine management guidelines.

### REFERENCES

1. The Global Alliance Against Chronic Respiratory Diseases (GARD). Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. Available at: [http://www.who.int/gard/publications/GARD\\_Manual/en/](http://www.who.int/gard/publications/GARD_Manual/en/). Accessed: 12 September, 2014.
2. Wedzicha JA 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. *The Lancet Respir Med*. 2013;1(3):199-209.
3. daCosta DiBonaventura M et al. The burden of chronic obstructive pulmonary disease among employed adults. *Int J Chron Obstruct Pulmon Dis*. 2012;7:211-9.
4. Fletcher MJ et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. *BMC Public Health*. 2011;11:612.
5. Rabe KF et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-55.
6. Matkovic Z et al. Predictors of adverse outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease. *Respiration*. 2012;84(1):17-26.
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2014. Available at: [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report2014\\_Feb07.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf). Accessed: 12 September, 2014.
8. Zhong N et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol/fluticasone combination (SFC) in patients with COPD: the LANTERN study. P2815. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
9. Wedzicha JA et al. QVA149 reduces the risk of moderate-to-severe exacerbations compared with open-label tiotropium in patients with severe COPD: the SPARK study. P898. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
10. Gessner C et al. Once-daily QVA149 improves lung function and dyspnoea compared with tiotropium plus formoterol: the QUANTIFY study. Poster P899. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
11. D'Urzo A et al. QVA149 improves dyspnoea and lung function versus tiotropium in symptomatic patients using LABA/ICS preceding study enrolment: the BLAZE study. Poster P2418. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
12. Mahler DA et al. Dual bronchodilation



- with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. *Eur Respir J*. 2014;43(6):1599-609.
13. Jones P et al. Examination of variations in responder rates in COPD clinical trial outcomes. *Eur Resp J*. 2013;42(Suppl 57):4152.
  14. D'Urzo A et al. Once-daily QVA149 improves dyspnoea, lung function and reduces rescue medication use in symptomatic patients with COPD using LAMA as prior medication: the BLAZE study. Poster P288. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  15. Hesselink AE et al. Determinants of an incorrect inhalation technique in patients with asthma or COPD. *Scand J Prim Health Care*. 2001;19(4):255-60.
  16. Lavorini F et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. *Respir Med*. 2008;102(4):593-604.
  17. Melani AS et al. Inhalation technique and variables associated with misuse of conventional metered-dose inhalers and newer dry powder inhalers in experienced adults. *Ann Allergy Asthma Immunol*. 2004;93(5):439-46.
  18. Kuttler A et al. A novel biophysical simulation model predicts consistent lung delivery of QVA149, glycopyrronium and indacaterol via the Breezhaler® device. P942. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  19. Gaebel K et al. Triple therapy for the management of COPD: a review. *COPD*. 2011;8(3):206-43.
  20. Vincken W et al. Free triple combination of glycopyrronium, indacaterol and ICS improves lung function and dyspnoea versus free double combination of indacaterol and ICS in patients with COPD: a post-hoc analysis from the GLOW6 study. P2410. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  21. Vincken W et al. Efficacy and safety of coadministration of once-daily indacaterol and glycopyrronium versus indacaterol alone in COPD patients: the GLOW6 study. *Int J Chron Obstruct Pulmon Dis*. 2014;9:215-28.
  22. Frith P et al. Glycopyrronium once-daily significantly improves lung function and health status when added to fluticasone/salmeterol in patients with COPD: the GLISTEN study. Poster P2811. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  23. Di Giovanni R et al. PSUR Safety profile of glycopyrronium in patients with COPD: an innovative approach to analyse data from post-marketing surveillance (PMS). P890. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  24. Buhl R et al. Once-daily tiotropium and olodaterol fixed-dose combination via the Respimat® improves outcomes vs mono-components in COPD in two 1-year studies. Abstract OP1895. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  25. Buhl R et al. Safety of once-daily tiotropium and olodaterol fixed-dose combination via the Respimat in chronic obstructive pulmonary disease in two 1-year studies. Poster P922. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  26. Watz H et al. The impact of stepwise withdrawal of inhaled corticosteroids on lung function in COPD patients receiving dual bronchodilation: WISDOM study. Poster P2423. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  27. Magnussen H et al. The impact of stepwise withdrawal of inhaled corticosteroids on exacerbations in COPD patients receiving dual bronchodilation: WISDOM study. Abstract 1890. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  28. Magnussen H et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med*. 2014;371(14):1285-94.
  29. Pascoe S et al. Blood eosinophil count as a biomarker of ICS effectiveness in reducing exacerbation rates in COPD. Poster P2817. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  30. Iqbal A et al. Is blood eosinophil count a predictor of response to bronchodilators in COPD? P2819. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  31. Worth H et al. Real life distribution of the COPD patients in GOLD stages A to D in German population (DACCORD registry). P929. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  32. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Revised 2011. Available at: [http://www.goldcopd.org/uploads/users/files/GOLD2011\\_Summary.pdf](http://www.goldcopd.org/uploads/users/files/GOLD2011_Summary.pdf). Accessed: 12 September, 2014.
  33. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD. Updated 2010. Available at: [http://www.goldcopd.org/uploads/users/files/GOLDReport\\_April112011.pdf](http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf). Accessed: 12 September, 2014.
  34. Vogelmeier C et al. Frequency of COPD exacerbations in the real-life out-patient DACCORD cohort. P930. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  35. Price D et al. Real-world prescribing patterns among newly diagnosed COPD patients receiving ICS: an analysis of UK patient dataset. P2422. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  36. Price D et al. Analyzing the pathway to triple therapy in COPD patients: a retrospective database analysis. P2411. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  37. Castellani W et al. An Italian, observational, multicenter trial to describe the therapeutic approach according to COPD GOLD guidelines during three years of observation: the MISTRAL study. P4013. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  38. Schino P et al. An Italian, observational, multicenter trial in female COPD patients: preliminary data on the women reality in the MISTRAL study. P4015. European Respiratory Society Annual Congress, Munich, Germany, 6-10 September, 2014.
  39. Asche CV et al. Adherence to current guidelines for chronic obstructive pulmonary disease (COPD) among patients treated with combination of long-acting bronchodilators or inhaled corticosteroids. *Int J Chron Obstruct Pulmon Dis*. 2012;7:201-9.
  40. Viegi G et al. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration*. 2001;68(1):4-19.
  41. Han MK et al. Gender and chronic obstructive pulmonary disease: why it matters. *Am J Respir Crit Care Med*. 2007;176(12):1179-84.
  42. Hurst JR et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128-38.
  43. Cote CG, Chapman KR. Diagnosis and treatment considerations for women with COPD. *Int J Clin Pract*. 2009;63(3):486-93.