Provided by
The France Foundation

FACULTY

Richard Casaburi, MD, PhD
David Geffen School of Medicine at UCLA
Los Angeles, California

Gary T. Ferguson, MD
Pulmonary Research Institute of Southeast Michigan
Farmington Hills, Michigan

David M. Mannino, MD
University of Kentucky College of Public Health
Lexington, Kentucky

AN UPDATE ON Fixed-Dose LAMA/LABA Inhalers in COPD

A CME SUPPLEMENT

ASK THE EXPERTS!

Visit www.PILOTforIPF.org/respirology to ask the authors questions

Contents

ASK THE EXPERTS!

Visit **www.PILOTforIPF.org/respirology** for an opportunity to ask the authors questions or to read questions from other learners. The authors will post answers every 2 weeks. Additional free online CME, downloadable slides, and resources are also available to pulmonologists, radiologists, and others who manage patients with pulmonary disease.

CME/CE Information

AUTHORS

Richard Casaburi, MD, PhD
David Geffen School of Medicine at UCLA
Los Angeles, California

Gary T. Ferguson, MD
Pulmonary Research Institute of Southeast Michigan
Farmington Hills, Michigan

David M. Mannino, MD
University of Kentucky College of Public Health
Lexington, Kentucky

Wendy Scales, PhD
The France Foundation
Old Lyme, CT

TARGET AUDIENCE

This activity is intended for health care professionals who treat and manage patients with COPD.

STATEMENT OF NEED

Inhaled long-acting bronchodilators are the cornerstone of maintenance therapy for patients with chronic obstructive pulmonary disease (COPD). A variety of long-acting muscarinic antagonists (LAMA) and long-acting β2-agonists (LABAs) are available for the management of COPD. An increasing number of fixed-dose LAMA/LABA combinations have been developed and approved; these combinations have the potential to provide synergistic effects through different mechanisms of action, maximize bronchodilation, and simplify COPD treatment regimens. In order to provide effective care and develop individualized treatment plans for patients with COPD, pulmonologists and other health care professionals who manage these patients need to be up to date with the latest information on the efficacy and safety of fixed-dose LAMA/LABA combinations.

LEARNING OBJECTIVES

Upon completion of the activity, participants should be able to:

- Evaluate key efficacy data from clinical trials on new and emerging fixed-dose LAMA/LABA inhalers in COPD.
- Evaluate key safety data from clinical trials on new and emerging fixed-dose LAMA/LABA inhalers in COPD.
- Apply information on the efficacy and safety of new/emerging LAMA/LABA inhalers in COPD to specific clinical scenarios.

You must request CME/CE credit at
www.PILOTforIPF.org/respirology

METHOD OF PARTICIPATION /HOW TO RECEIVE CREDIT

1. There are no fees for participating in and receiving credit for this activity.
2. Review the activity objectives and CME/CE information.
3. Complete the CME/CE activity
4. Complete the online posttest. A score of at least 75% is required to successfully complete this activity. The participant may take the test until successfully passed.
5. Complete the CME/CE evaluation/attestation form, which provides each participant with the opportunity to comment on how participating in the activity will affect their professional practice; the quality of the instructional process; the perception of enhanced professional effectiveness; the perception of commercial bias; and his/her views on future educational needs.
6. Credit documentation/reporting: If you are requesting *AMA PRA Category 1 Credits*™ or a certificate of participation—your CME/CE certificate will be available for download.

Release Date: September 30, 2016

Expiration Date: September 29, 2017

Estimated Time to Complete Activity:
2 hours

ACCREDITED PROVIDER

This activity is provided by The France Foundation

ACCREDITATION STATEMENT

The France Foundation is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION

The France Foundation designates this enduring activity for a maximum of 2.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE POLICY

In accordance with the ACCME Standards for Commercial Support, The France Foundation (TFF) requires that individuals in a position to control the content of an educational activity disclose all relevant financial relationships with any commercial interest. TFF resolves all conflicts of interest to ensure independence, objectivity, balance, and scientific rigor in all its educational programs. Furthermore, TFF seeks to verify that all scientific research referred to, reported, or used in a CME/CE activity conforms to the generally accepted standards of experimental design, data collection, and analysis. TFF is committed to providing learners with high-quality CME/CE activities that promote improvements in health care and not those of a commercial interest.

ACTIVITY STAFF DISCLOSURES

The planners, reviewers, editors, staff, CME committee, or other members at The France Foundation who control content have no relevant financial relationships to disclose.

FACULTY DISCLOSURES– CONTENT CREATORS AND ACTIVITY FACULTY

The following faculty report that they have relevant financial relationships to disclose:

- **Richard Casaburi, MD, PhD,** has received grants/research support from Astellas, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., and Pulmonx. He has served as a consultant for Astellas, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, and Novartis. Dr. Casaburi is a stock shareholder of Inogen, Inc. He has received honoraria from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Novartis, and Sunovion.
- **Gary T. Ferguson, MD,** has served as a consultant for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Meda, Mylan, Novartis, Pearl Therapeutics, Sunovion, Theravance, and Verona. He has also received honoraria from Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, Meda, and Sunovion.
- **David M. Mannino, MD,** has received grants/research support from GlaxoSmithKline. He has served as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, Mylan, and Novartis. Dr. Mannino has received honoraria from Boehringer Ingelheim Pharmaceuticals, Inc. and Sunovion. He has received other financial or material support from Up-to-Date.
- **Wendy Scales, PhD,** has nothing to disclose.

DISCLOSURE OF UNLABELED USE

TFF requires CME faculty (authors) to disclose when products or procedures being discussed are off label, unlabeled, experimental, and/or investigational, and any limitations on the information that is presented, such as data that are preliminary, or that represent ongoing research, interim analyses, and/or unsupported opinion. Faculty in this activity may discuss

information about pharmaceutical agents that is outside of US Food and Drug Administration approved labeling. This information is intended solely for continuing medical education and is not intended to promote off-label use of these medications. TFF does not recommend the use of any agent outside of the labeled indications. If you have questions, contact the Medical Affairs Department of the manufacturer for the most recent prescribing information.

COMMERCIAL SUPPORT ACKNOWLEDGMENT

This activity is supported by an educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

DISCLAIMER

The France Foundation presents this information for educational purposes only. The content is provided solely by faculty who have been selected because of recognized expertise in their field. Participants have the professional responsibility to ensure that products are prescribed and used appropriately on the basis of their own clinical judgment and accepted standards of care. The France Foundation and the commercial supporter assume no liability for the information herein.

COPYRIGHT INFORMATION

PRIVACY POLICY

The France Foundation protects the privacy of personal and other information regarding participants and educational collaborators. The France Foundation will not release personally identifiable information to a third party without the individual's consent, except such information as is required for reporting purposes to the ACCME.

The France Foundation maintains physical, electronic, and procedural safeguards that comply with federal regulations to protect against the loss, misuse or alteration of information that we have collected from you.

Additional information regarding The France Foundation's Privacy Policy can be viewed at http://www.francefoundation.com/privacy.

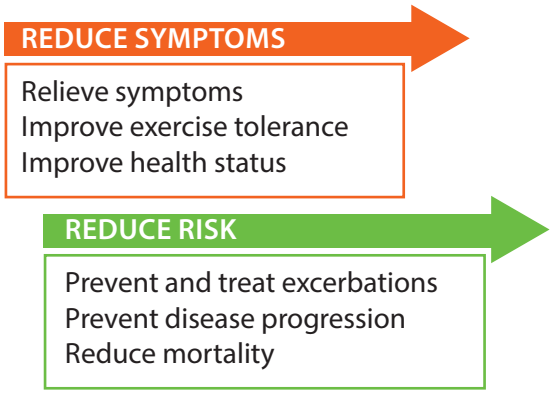
CONTACT INFORMATION

If you have questions about this CME activity, please contact The France Foundation at 860-434-1650 or info@francefoundation.com.

Introduction

According to the World Health Organization, an estimated 65 million people worldwide have moderate-to-severe chronic obstructive pulmonary disease (COPD).[1] In the United States, the American Lung Association reports that more than 11 million Americans have been diagnosed with COPD and COPD ranks as the third leading cause of death.[2] As outlined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, treatment of COPD embodies two overarching goals: to reduce the impact of symptoms and to reduce the risk of adverse health events (Figure 1).[3]

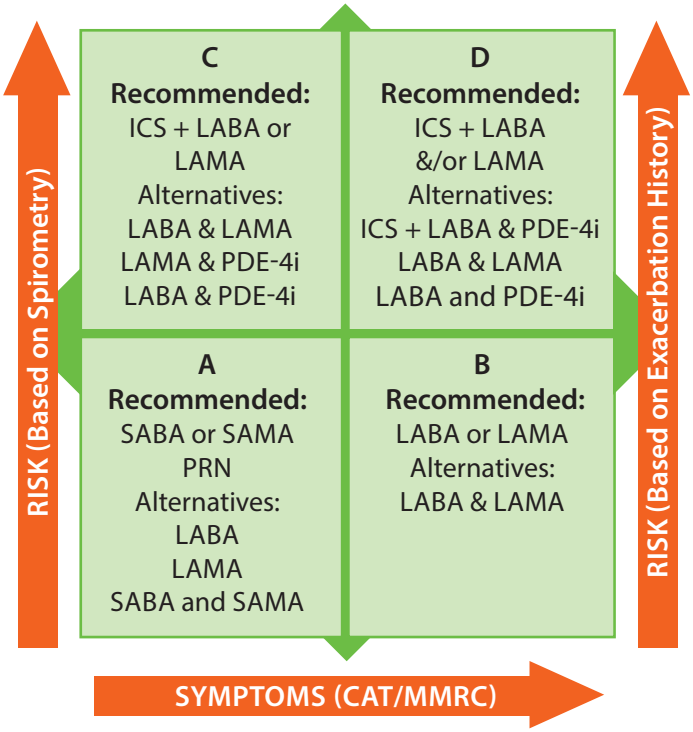
Figure 1: Goals of Management of COPD: GOLD Guidelines



Inhaled long-acting bronchodilators are a cornerstone of pharmacologic management of patients with COPD. According to the GOLD guidelines, these agents are included in the recommended treatment options for patients meeting criteria for GOLD groups B, C, or D, and may even be considered as a treatment option in select GOLD A patients (Figure 2).[3]

Long-acting muscarinic antagonists (LAMAs), including aclidinium, glycopyrronium (glycopyrrolate), tiotropium, and umeclidinium exert their benefits in patients with COPD primarily through M_3 receptor subtype binding and blockade of acetylcholine-mediated bronchoconstriction.[4] Long-acting β2-agonists (LABAs) provide direct relaxant activity on airway smooth muscle via β2 adrenoceptors.[4] Indacaterol, formoterol, olodaterol, salmeterol and vilanterol are LABAs commonly used for patients with COPD. While LAMA and LABA monotherapies have clear benefits for improving lung function in patients with COPD, there is increasing interest in fixed-dose LAMA/LABA

Figure 2: GOLD COPD Treatment Approach (adapted)[3]



Abbreviations: ICS: inhaled corticosteroid; LABA: long acting β2-agonist; LAMA: long-acting muscarinic antagonist; PDE-4i: phosphodiesterase -4 inhibitor; SABA: short-acting β2-agonist; SAMA: short-acting muscarinic antagonist; CAT: COPD Assessment Test; mMRC: modified British Medical Research Council scale

combinations.[5] Among the proposed benefits for these combinations are the potential to increase bronchodilation through distinct and complementary mechanisms of action, the possibility of lower risk of side effects compared with increased doses of monotherapies, and simplification of treatment regimens. Several fixed-dose LAMA/LABA combinations are currently approved in the United States and abroad (Table 1). It should be noted that there are differences in trade names, doses and dosing frequency for some of these combinations depending on the country of product approval.

Table 1: Inhaled Fixed-Dose LAMA/LABA Combinations for COPD[5,6,7]

Name	Location (Approval Date)	Administration Frequency/ Dose	Inhalation Device
Once Daily Dosing			
Umeclidinium/vilanterol Anoro® Ellipta®	US (2013)	Once daily 62.5 µg/25 µg per dose	Dry powder inhaler
Umeclidinium/vilanterol Anoro Ellipta	Europe, Japan, Australia, and other non-US countries (2014)	Once daily 62.5 µg/25 µg per dose	Dry powder inhaler
Tiotropium/olodaterol Stiolto™ Respimat®	US (2015)	Two inhalations (one dose) once daily 5 µg /5 µg per dose	Soft mist inhaler
Tiotropium/olodaterol Spiolto Respimat	Europe (2015)	Two inhalations (one dose) once daily 5 µg /5 µg per dose	Soft mist inhaler
Indacaterol/ glycopyrronium Ultibro Breezhaler	Europe, Japan (2013)	Once daily 110 µg/50 µg	Dry powder inhaler
Twice Daily Dosing			
Indacaterol/glycopyrrolate Utibron™ Neohaler®	US (2015)	Twice daily 27.5 µg/15.6 µg per dose	Dry powder inhaler
Glycopyrrolate/formoterol Bevespi Aerosphere™	US (2016)	Two inhalations (one dose) twice daily 18 µg/9.6 µg per dose	Pressurized metered dose inhaler
Aclidinium/formoterol Brimica Genuair (also Duaklir Genuair)	Europe (2014)	Twice daily 400 µg/12 µg per dose	Dry powder inhaler

In this article, we will provide a review of the efficacy and safety from key clinical trials of these fixed-dose combination (FDC) bronchodilators for patients with COPD.

Efficacy and Safety of Fixed-Dose LAMA/LABA Combinations

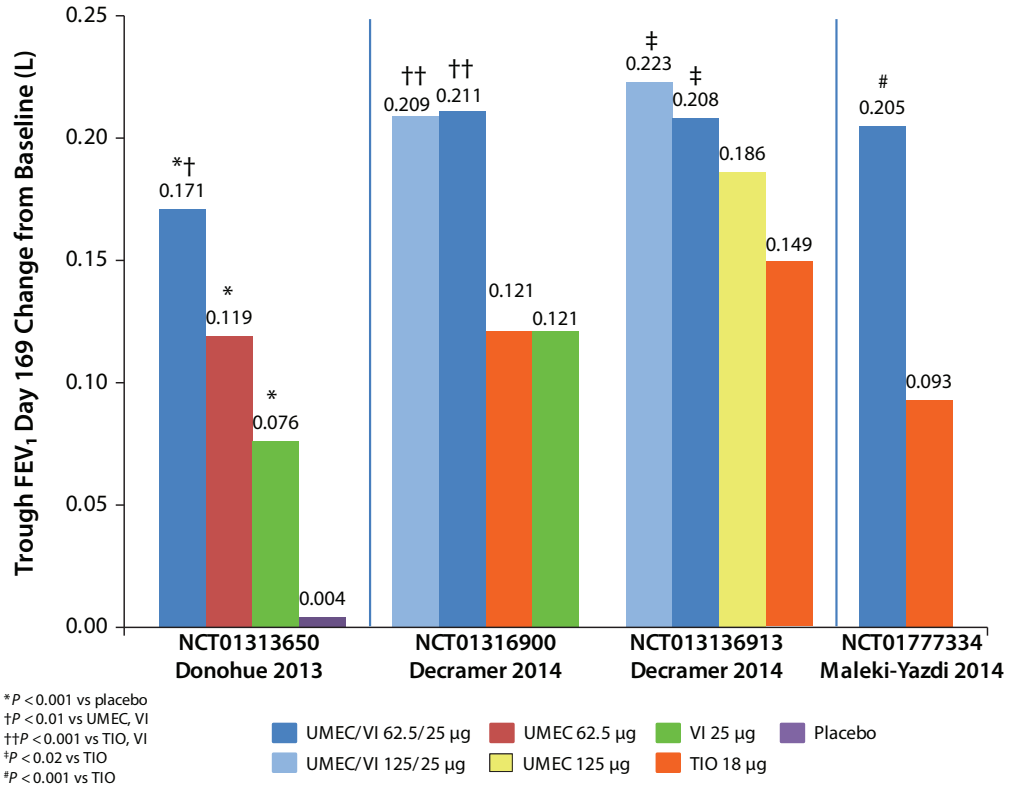
UMECLIDINIUM/VILANTEROL

Umeclidinium/vilanterol (UMEC/VI) is a once-daily inhaled fixed-dose LAMA/LABA combination delivered by dry powder inhaler (62.5/25 µg per dose) approved as a maintenance treatment for patients with COPD.[8] The safety and efficacy of UMEC/VI have been evaluated in several 12 and 24 week studies, comparing the fixed-dose combination with placebo, monocomponents, or an active comparator.[9,10,11]

Lung Function In 2013, Donohue et al. reported the results of a 24-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled trial (N = 1532 randomized) evaluating once daily UMEC/VI FDC versus monocomponents and placebo in patients with moderate-to-severe COPD.[9]

This study demonstrated superiority of UMEC/VI FDC (62.5/25 µg) for the primary endpoint, trough FEV_1 at Day 169, compared with placebo and monocomponents (UMEC 62.5 µg and VI 25 µg) **(Figure 3)**.[9] The treatment difference between UMEC/VI FDC (62.5/25 µg) and UMEC (62.5 µg) and VI (25 µg) was 0.052L and 0.095L,

Figure 3: Umeclidinium/Vilanterol Fixed-Dose Combination: Improvement in Trough FEV_1[9,10,11]



*P < 0.001 vs placebo
†P < 0.01 vs UMEC, VI
††P < 0.001 vs TIO, VI
‡P < 0.02 vs TIO
#P < 0.001 vs TIO

UMEC: umeclidinium; VI: vilanterol; PBO: placebo; TIO: tiotropium

respectively ($P < 0.01$ and $P < 0.001$).[9] UMEC (62.5 µg) and VI (25 µg) monotherapies were also associated with significant improvement vs placebo in the primary endpoint. Additional studies have demonstrated improvement in lung function with UMEC/VI FDC. Decramer et al. reported the results of two 24-week, randomized, blinded, active-controlled studies comparing two doses of once daily UMEC/VI FDC (125/25 µg; 62.5/25 µg), tiotropium (TIO, 18 µg), and either VI (25 µg) or UMEC (125 µg) in patients with moderate-to-very severe COPD.[10] A combined total of 1818 patients were randomized in these studies. As shown in **Figure 3**, both doses of UMEC/VI FDC were associated with significant improvement in lung function (assessed as trough FEV_1 on Day 169) vs its monocomponents and with TIO.[10] An additional 24-week, randomized controlled trial reported by Maleki-Yazdi et al. compared once daily UMEC/VI FDC (62.5/25 µg) with TIO (18 µg) in patients with moderate to very severe COPD (N = 905 patients randomized).[11] In this study, treatment with UMEC/VI FDC resulted in a significant improvement in the primary endpoint vs TIO, with a trough FEV_1 at Day 169 treatment difference of 0.112 L **(Figure 3)**. The UMEC/VI FDC was also associated with significant improvement in other lung function parameters vs TIO, including 0-6 hour weighted mean FEV_1 at Day 168 (0.276 vs 0.170 L, respectively; $P < 0.001$) and time to onset of action (FEV_1 improvement) during 0-6 hour post dose at Day 1 (19 vs 31 minutes, respectively; $P < 0.001$). [11]

Dyspnea and HRQL In the 24-week placebo controlled study, active treatments were associated with significant improvement in transition dyspnea index (TDI) focal scores at Day 168 compared to placebo (treatment differences for UMEC/VI FDC (62.5/25 µg), UMEC (62.5 µg), and VI (25 µg) vs placebo were 1.2, 1.0, and 0.9, respectively).[9] Decramer et al also reported meaningful improvement in TDI at Day 168 for both doses of UMEC/VI FDC (125/25 µg; 62.5/25 µg), UMEC (62.5 µg), VI (25 µg), and TIO (18 µg) monotherapies.[10] Differences between UMEC/VI FDC and comparators in these studies were small and not significant.

Improvement in health-related quality of life (HRQL), as measured by St. George's Respiratory Questionnaire (SGRQ), was clinically meaningful (i.e., a decrease of 4 units) at Day 168 for UMEC/VI FDC (62.5/25 µg), UMEC (62.5 µg), and VI (25 µg) compared with placebo; treatment differences were -5.51, -4.69, and -5.19, respectively.[9] Importantly, the changes in SGRQ associated with UMEC/VI FDC treatment compared with UMEC (62.5 µg) and VI (25 µg) were small (-0.82 and -0.32, respectively) and were not statistically or clinically significant. Similarly, Decramer et al reported that all active treatments resulted in a change from baseline to Day 168 in SGRQ > 4.0, but there were no significant differences between UMEC/VI FDC, UMEC, VI, or TIO treatment groups.[10] In the 24-week study comparing UMEC/VI FDC (62.5/25 µg) vs TIO (18 µg), SGRQ scores at Day 168 were -7.27 for the UMEC/VI FDC compared with -5.17 with TIO, a -2.10 treatment difference ($P = 0.006$).[11]

Rescue Medication In the placebo-controlled study, Donohue et al reported that all active treatments were associated with less rescue salbutamol use compared with placebo over the 24 week study.[9] In a 24-week study comparing UMEC/VI FDC (62.5/25 µg) with TIO monotherapy, once daily treatment with UMEC/VI FDC resulted in significantly less rescue albuterol/salbutamol use over the 24-week study compared with TIO (-1.3 vs -0.8 puffs/day, $P < 0.001$).[11]

Exercise Capacity Exercise endurance in patients with moderate-to-severe COPD was evaluated with two doses of UMEC/VI FDC (125/25 µg or

62.5/25 µg) in two, 12-week, double-blind, placebo-controlled cross-over studies.[12] Post-hoc integrated analysis of these studies demonstrated a significant change from baseline in exercise endurance time with the endurance shuttle walking test for both UMEC/VI FDC doses compared with placebo at 12 weeks ($P < 0.01$). These differences (47.5 s for UMEC/VI 125/25 µg and 43.7 s for UMEC/VI 62.5/25 µg) were near the lower bounds of the hypothesized minimal clinically important difference of 45-85 seconds for this exercise test.[12] Integrated analysis of trough FEV_1 change from baseline demonstrated greater changes for both doses of UMEC/VI FDC vs placebo in these studies.[12]

Safety and Tolerability In each of the above mentioned studies, UMEC/VI FDC was well tolerated. Donohue et al. reported on-treatment adverse events (AEs) in 51% of patients in the UMEC/VI (62.5/25 µg) treatment group compared with 46% for placebo, 52% UMEC (62.5 µg), and 48% VI (25 µg).[9] AEs leading to discontinuation of study medication were reported for 6% in the UMEC/VI (62.5/25 µg) group compared with 3%, 8%, and 6% in the placebo, UMEC, and VI groups respectively. Incidence of AEs was similar for UMEC/VI (62.5/25 µg) and TIO (18 µg) active control in a 24 week study (44% and 42%, respectively), with 4% AEs leading to discontinuation with UMEC/VI FDC compared with 3% for TIO.[11] Headache and nasopharyngitis were the most commonly reported AEs (ranging from ~4-11%) across treatment groups (UMEC/VI, UMEC, VI, TIO and placebo) in the 24-week studies. Naccarelli et al. evaluated the cardiovascular safety of once daily UMEC/VI FDC from 8 clinical trials in patients with COPD.[13] In this pooled analysis, no clinically relevant increase in major adverse cardiovascular events (MACE) or CV events of special interest (AESI) were apparent with UMEC/VI FDC (125/25 µg or 62.5/25 µg), UMEC (125 µg or 62.5 µg) or VI (25 µg) compared with placebo.[13]

TIOTROPIUM/OLODATEROL

Tiotropium/olodaterol fixed-dose combination (TIO/OLO, 2 inhalations per dose, each dose = 5/5 µg) is a once daily inhaled maintenance treatment approved for patients with COPD.[14] The safety and efficacy of TIO/OLO FDC have been studied in 12- and 52-week studies.[15,16] TONADO-1 and TONADO-2 were replicate multinational, phase 3, randomized, double-blind, active-controlled, 52-week trials.[16] These trials had three primary endpoints: FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1 response, and SGRQ total score at 24 weeks. Patients with moderate to very severe COPD (GOLD 2-4) were randomized to one of five once daily treatment groups; TIO/OLO FDC (2.5/5 µg), TIO/OLO FDC (5/5 µg), TIO (2.5 µg), TIO (5 µg), or OLO (5 µg). A combined total of 5162 patients received treatment in the TONADO studies. OTEMTO 1 and 2 were replicate, 12 week, phase 3 studies including a placebo arm investigating the effects of TIO/OLO FDC on lung function and quality of life in patients with moderate-to-severe COPD.[15] A total of 1623 patients in the OTEMTO studies were randomized to one of 4 daily treatments: TIO/OLO FDC (5/5 µg), TIO/OLO FDC (2.5/5 µg), TIO (5 µg), or placebo. Primary endpoints in the OTEMTO trials were SGRQ total score, FEV_1 AUC_{0-3} change from baseline, and trough FEV_1 response at 12 weeks.[15]

Lung Function Significant improvement in FEV_1 AUC_{0-3} was demonstrated with both TIO/OLO FDC doses in the TONADO and OTEMTO studies compared with individual components or placebo **(Table 2)**.[15,16] In TONADO-1 and TONADO-2, both doses of the TIO/OLO FDC were superior to monocomponents in trough FEV_1 at 24 weeks. In the OTEMTO studies, the TIO/OLO FDC (both doses) was superior to placebo in both

Table 2: Tiotropium/Olodaterol FDC Lung Function (TONADO and OTEMTO Studies)[15,16]

Treatment Comparison	Adjusted Mean FEV_1 AUC_{0-3}, L (95% CI)	Adjusted Mean Trough FEV_1, L (95% CI)
TONADO-1 and TONADO-2, Combined Analysis, 24 weeks		
TIO/OLO (5/5 µg)		
vs OLO (5 µg)	0.128 (0.111, 0.144)*	0.085 (0.067, 0.102)*
vs TIO (5 µg)	0.110 (0.093, 0.127)*	0.060 (0.043, 0.077)*
TIO/OLO (2.5/5 µg)		
vs OLO (5 µg)	0.115 (0.098, 0.131)*	0.062 (0.045, 0.080)*
vs TIO (2.5 µg)	0.111 (0.095, 0.128)*	0.045 (0.028, 0.062)*
vs TIO (5 µg)	0.097 (0.080, 0.113)*	0.038 (0.021, 0.055)*
OTEMTO-1 and OTEMTO-2, 12 weeks (values for both studies are listed)		
TIO/OLO (5/5 µg)		
vs placebo	0.331 (0.293, 0.369)* 0.299 (0.261, 0.336)*	0.162 (0.124, 0.200)* 0.166 (0.129, 0.203)*
vs TIO (5 µg)	0.111 (0.075, 0.148)* 0.105 (0.069, 0.141)*	0.028 (-0.009, 0.066) 0.039 (0.002, 0.076)**
TIO/OLO (2.5/5 µg)		
vs placebo	0.300 (0.262, 0.337)* 0.284 (0.246, 0.323)*	0.150 (0.113, 0.188)* 0.169 (0.132, 0.207)*
vs TIO (5 µg)	0.080 (0.044, 0.116)* 0.091 (0.053, 0.128)*	0.017 (-0.021, 0.054) 0.042 (0.005, 0.079)**

*$P < 0.0001$; **$P < 0.05$

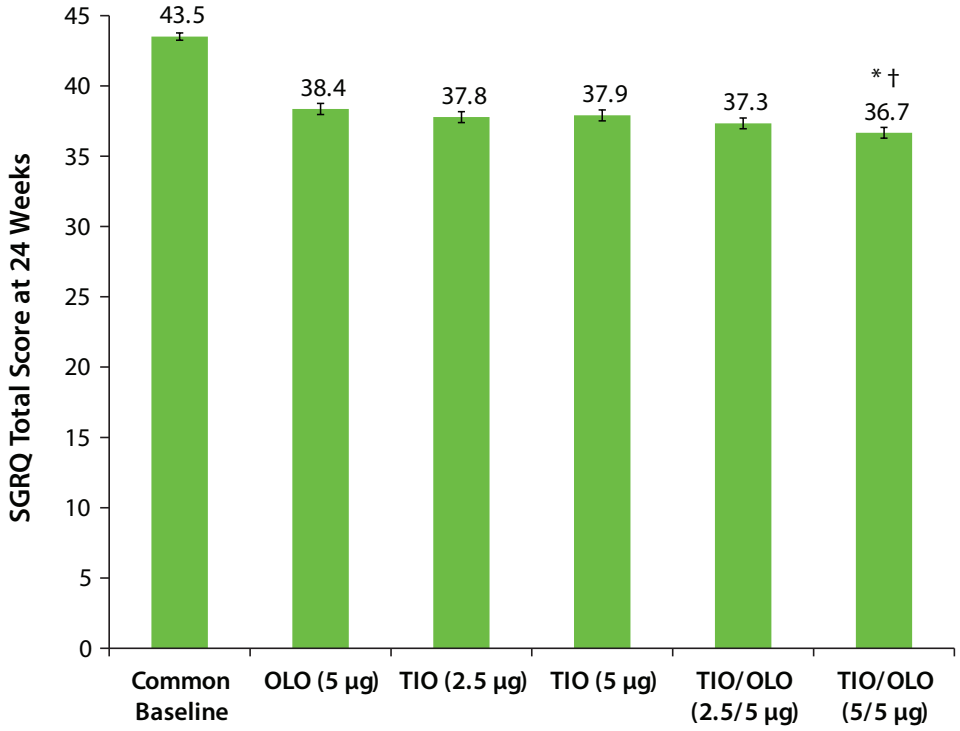
studies, but significant improvement compared with TIO monotherapy was only demonstrated in OTEMTO 2 (Table 2).[15]

In a post-hoc analysis of the TONADO-1 and TONADO-2 studies, Ferguson et al. demonstrated statistically significant benefits of TIO/OLO FDC (5/5 µg) on lung function parameters vs monocomponents in subgroup analysis of patients with GOLD 2 and GOLD 3-4 disease.[17]

These treatment effects were also independent of prior LAMA or LABA maintenance therapy. The authors noted that the magnitude of lung function improvement (FEV_1 AUC_{0-3} and trough FEV_1) with TIO/OLO (5/5 µg) FDC relative to baseline was generally greater for those patients with less severe disease.[17]

Singh et al. performed a post hoc analysis of the OTEMTO studies, to assess benefits associated

Figure 4: TONADO-1 and TONADO-2: St. George's Respiratory Questionnaire Score[16]



*$P < 0.01$ vs OLO (5 µg); †$P < 0.05$ vs TIO (5 µg)

with TIO/OLO FDC (5/5 µg) vs placebo or TIO monotherapy according to lung function (GOLD 2 or 3), GOLD combined assessment (A, B, C, D), and treatment history.[18] This subgtroup analysis showed that TIO/OLO FDC is equally effective for patients with moderate and severe disease; and benefits on lung function were independent of GOLD A, B, C, or D categorization. Improvements in SGRQ associated with TIO/OLO FDC (5/5 µg) treatment compared with TIO monotherapy were most notable in patients with COPD categorized as GOLD B. The superiority of TIO/OLO FDC (5/5 µg) over TIO in lung function was independent of prior treatment history.[18]

Dyspnea and HRQL In the TONADO studies, combined analysis of TDI scores at 24 weeks indicated that treatment with both of the TIO/OLO FDC doses resulted in significant improvement compared with the respective monotherapies ($P < 0.05$ for all comparisons). All treatments in the TONADO-1 and TONADO-2 studies were associated with clinically meaningful improvement in HRQL (SGRQ) at 24 weeks relative to baseline **(Figure 4)**. TIO/OLO (5/5 µg) was associated with statistically significant improvement in SGRQ total scores at 24 weeks vs monocomponents (-1.693 and -1.233 vs OLO (5 µg) and TIO (5 µg), respectively).[16] The treatment effects observed with the lower TIO/OLO FDC (2.5/5 µg) dose vs the monocomponents did not reach significance.

In the OTEMTO 1 and 2 studies, treatment with TIO/OLO FDC (5/5 µg) was associated with statistically significant improvement in SGRQ total score at 12 weeks vs placebo and TIO (5 µg) monotherapy (4.89 and 4.56 vs placebo; 2.49 and 1.72 vs TIO for OTEMTO 1 and OTEMTO 2, respectively). Treatment with the lower dose of TIO/OLO FDC (2.5/5 µg) resulted in significant improvement in SGRQ vs placebo in OTEMTO 1 and OTEMTO 2 (4.12 and 3.67, respectively), but

not compared with TIO monotherapy.[15]

Rescue Medication Rescue medication use in the TONADO studies was reduced with TIO/OLO FDC (2.5/5 µg and 5/5 µg) vs monotherapies beginning at Study Week 1 and continuing through completion at Week 52.[19]

Composite Endpoint–Clinically Significant Events Buhl et al. conducted a post hoc analysis of the TONADO-1 and TONADO-2 studies to determine if the TIO/OLO FDC (5/5 µg) was more effective in delaying a composite clinically significant event endpoint in patients with GOLD B COPD compared with TIO (5 µg) monotherapy.[20] In this analysis, the composite endpoint incorporated time to first reduction in trough FEV_1 from baseline ≥ 100 mL, time to first increase in SGRQ total score from baseline ≥ 4.0, or time to moderate or severe exacerbations.[20] TIO/OLO FDC (5/5 µg) was associated with significantly longer time to clinically important deterioration compared with TIO (5 µg) (HR 0.68 (0.56-0.83); $P < 0.001$).[20] For individual components, trough FEV_1 decline from baseline ≥ 100 mL was 226 days for TIO/OLO (5/5 µg) vs 91 days for TIO (5 µg); SGRQ score increase from baseline ≥ 4.0 units was 369 days vs 175, respectively.[20]

Exacerbations While exacerbation rate was not a primary or secondary endpoint in the TONADO studies, Derom et al. conducted a post hoc analysis of exacerbations/time to first exacerbation in the TIO/OLO (5/5 µg), TIO (5 µg), and OLO (5 µg) arms of the TONADO-1 and TONADO-2 studies.[21] Data from 3,100 patients were evaluable; results are summarized in Table 3. Once daily treatment with TIO/OLO FDC (5/5 µg) was associated with significantly reduced risk of moderate/severe exacerbations vs. OLO, but not TIO (HR 0.834 vs OLO (5 µg), $P = 0.03$; HR 0.925 vs TIO (5 µg), NS).[21]

Safety and Tolerability Analysis of safety data from both TONADO-1 and TONADO-2 studies indicated that incidence of AEs was balanced across treatment groups; overall 74% of patients reported at least one AE.[16] Treatment-related AEs ranged from 6.0 to 7.1%. AEs leading to discontinuation occurred in 7.4% of patients in the TIO/OLO (5/5 µg) group, 5.5% in TIO/OLO (2.5/5 µg), 9.0% for TIO (5 µg), 8.7% for TIO (2.5 µg), and 9.9% for OLO (5 µg).[16] Infections, COPD exacerbations, and nasopharyngitis were the most commonly reported AEs, with similar frequencies across treatment groups. Incidence of MACE and cardiac disorders were similar across treatment groups.

INDACATEROL/GLYCOPYRROLATE

Readers should note when reviewing the literature on inhaled indacaterol/glycopyrrolate (IND/GLY) FDC for patients with COPD that the products and dosing frequency are different between the United States and other parts of the

Table 3: TONADO-1 and TONADO-2: COPD Exacerbations[21]

Treatment Group	Moderate or Severe Exacerbations, 52 Weeks (%)	Time to 1st Moderate or Severe Exacerbation (days)	Annual Exacerbation Rate (per patient per year)
TIO/OLO (5/5 µg)	27.7	296	0.471
TIO (5 µg)	28.8	270	0.509
OLO (5 µg)	31.9	220	0.564

world. In countries within the EU, Japan, Australia, and other countries outside of the US, IND/GLY (110/50 µg) is approved as a ***once daily*** treatment delivered as a dry powder inhaler.[22] In contrast, in the US, IND/GLY (27.5/15.6 µg) was developed and approved as an inhaled ***twice daily*** FDC for patients with COPD.[23] An additional note: glycopyrrolate and glycopyrronium are identical drugs. The dose of glycopyrrolate is calculated with its bromide salt (15.6 µg and 31.2 µg); the dose of glycopyrronium is calculated without its bromide salt (12.5 µg and 25 µg, respectively).[24]

ONCE DAILY IND/GLY FDC (110/50 µg)

The safety and efficacy of once daily IND/GLY (110/50 µg) FDC in patients with COPD have been demonstrated in multiple phase 3 trials.[25] Rodrigo et al. published a systematic review of five randomized, placebo-controlled, or crossover trials ranging in duration from 3-64 weeks, and including 4,842 patients with COPD.[26] This analysis demonstrated superior efficacy of once daily IND/GLY (110/50 µg) compared with once daily GLY (50 µg) or TIO (18 µg).

Lung Function Treatment with IND/GLY (110/50 µg) was associated with significant improvements in mean change from baseline in trough FEV_1 compared with GLY (50 µg) monotherapy (70 mL, $P < 0.0001$ at weeks 12 and 26), and also compared with TIO (18 µg) (range 60-100 mL, $P < 0.001$).[26]

Dyspnea and HRQL This analysis also demonstrated that the mean change from baseline of SGRQ total score was higher for IND/GLY (110/50 µg) compared with GLY (50 µg) or TIO (18 µg), with treatment differences -2.18 and -2.64 units, respectively, ($P < 0.04$ for both comparisons).[26] Compared with both GLY (50 µg) and TIO (18 µg) monotherapies, once daily IND/GLY (110/50 µg) was associated with a greater percentage of patients achieving a minimal clinically important difference in SGRQ ≥ 4.0 units.

Exacerbations and Rescue Medication Fewer COPD exacerbations were noted with the IND/GLY (110/50 µg) FDC vs GLY (50 µg) or TIO (18 µg) monotherapies, and a significant reduction in the use of rescue medication was reported with once daily IND/GLY (110/50 µg) vs the monotherapies (-0.59 and -0.63 puffs/day vs GLY and TIO, respectively, $P < 0.0001$ for both comparisons).[26]

Safety and Tolerability This systematic review noted no significant differences in the rate of AEs or withdrawals due to AEs among the treatment groups.[26]

The FLAME Study Results of the FLAME study were recently published by Wedzicha et al.[27] This 52-week, randomized, double-blind, double-dummy, noninferiority trial evaluated the effect of once daily IND/GLY (110/50 µg) vs a twice daily LABA inhaled steroid combination: salmeterol (50 µg) plus fluticasone (500 µg) [SAL/FLU (50/500 µg)] on COPD exacerbations. The primary endpoint was the annual rate of all COPD exacerbations (including mild, moderate or severe). A total of 3,362 patients who had a history of at least one exacerbation during the previous year were randomized to IND/GLY (110/50 µg) or SAL/FLU (50/500 µg) treatment groups.[27] The annual rate of all exacerbations was 3.59 in the IND/GLY treatment group compared with 4.03 in the SAL/FLU treatment group, reflecting an 11% reduction, $P = 0.003$ (rate ratio 0.89; 95% CI 0.83 - 0.96). IND/GLY treatment resulted in a 17% lower rate of moderate or severe exacerbations vs SAL/FLU (0.98 vs 1.19; rate ratio 0.83; 95% CI 0.75-0.91, $P < 0.001$). In subgroup analysis, the benefit with once daily IND/GLY on rate of all exacerbations reached

statistical significance in patients with 1 exacerbation in the previous year (rate ratio 0.87; 95% CI 0.81-0.95), but not for those with ≥ 2 exacerbations (rate ratio 0.89, 95% CI 0.76-1.05), the group of patients for which the use of inhaled corticosteroids with a long acting bronchodilator is recommended. Treatment with IND/GLY (110/50 µg) was associated with longer time to first exacerbation relative to SAL/FLU (50/500 µg), 71 vs 51 days, respectively, $P < 0.001$).[27]

Exercise Capacity The MOVE Study, a multicenter, randomized, double-blind, placebo-controlled crossover study assessed the effect of once daily IND/GLY (110/50 µg) compared with placebo on lung hyperinflation (assessed by inspiratory capacity, IC) and physical activity (assessed by accelerometry) in patients with moderate to severe COPD.[28] Patients were treated with once daily IND/GLY (110/50 µg) or placebo in two 21-day treatment periods, separated by a 14-day washout between periods.[28] The primary endpoints were peak IC and average daily activity-related energy expenditure. One hundred ninety-four patients were randomized, and treatment with IND/GLY (110/50 µg) was associated with a significant increase in peak IC after 21 days vs placebo (treatment difference, 202 mL, $P < 0.0001$).[28] Activity-related energy expenditure increased with IND/GLY treatment (36.7 kcal/day treatment difference vs placebo, $P = 0.04$), and the average number of steps per day also increased (358 step treatment difference vs placebo, $P = 0.029$).[28]

TWICE DAILY IND/GLY FDC (27.5/15.6 µg)

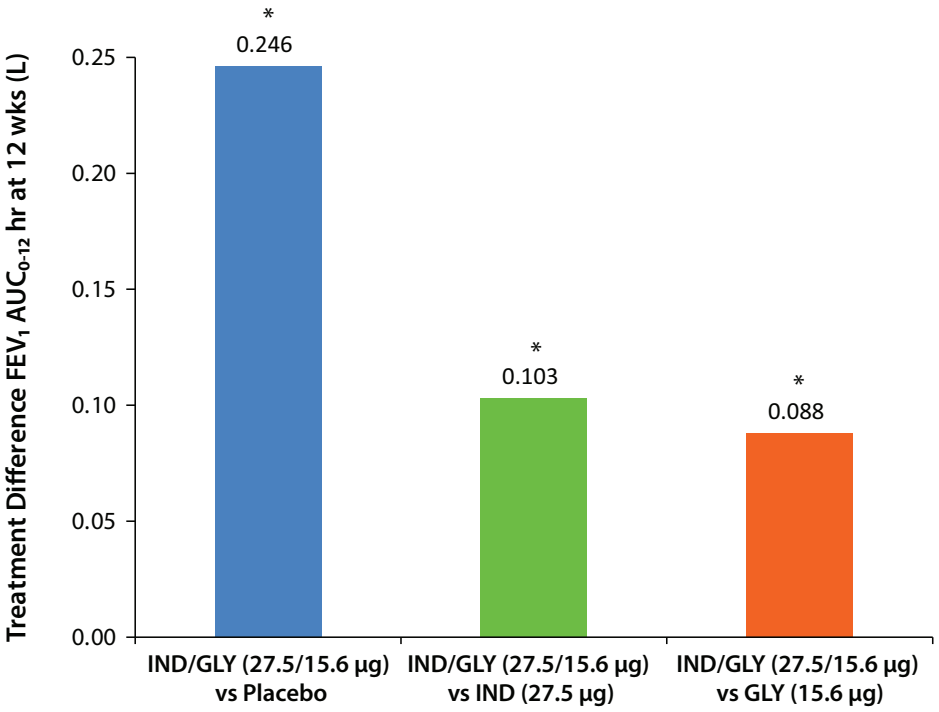
The United States IND/GLY (27.5/15.6 µg), twice daily FDC approval was based on multiple clinical trials, including FLIGHT1, 2, and 3 phase 3 studies.[24] FLIGHT1 and FLIGHT2 were identical 12-week, randomized, double-blind, parallel-group, placebo and active-controlled studies comparing twice daily IND/GLY (27.5/15.6 µg) vs monocomponents and placebo in patients with moderate-to-severe COPD.[29] The primary objective of FLIGHT1 and FLIGHT2 was to demonstrate superiority of IND/GLY (27.5/15.6 µg BID) FDC vs monocomponents on FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) at study Week 12. Pooled results of FLIGHT1 and FLIGHT2 reported by Mahler et al. included a total of 2,038 patients.[29]

Lung Function At 12 weeks, twice daily IND/GLY (27.5/15.6 µg) FDC was superior to the monocomponents and placebo in FEV_1 AUC_{0-12} **(Figure 5)**. Twice daily treatment with IND (27.5 µg) and GLY (15.6 µg) monotherapies resulted in significant improvement in FEV_1 AUC_{0-12} at Week 12 vs placebo (treatment difference 0.143 L and 0.158 L, respectively; $P < 0.001$).[29] Treatment with twice daily IND/GLY (27.5/15.6 µg) also resulted in significant improvement in peak and trough FEV_1 at Week 12 compared with the individual components and placebo.

Dyspnea and HRQL Symptomatic benefit associated with twice daily IND/GLY (27.5/15.6 µg) was demonstrated in SGRQ total scores at Week 12 vs placebo (-5.0 treatment difference, $P < 0.001$); improvement relative to IND (27.5 µg) and GLY (15.6 µg) monotherapies was statistically significant, but the treatment difference did not achieve the minimal clinically important difference of a 4.0 unit reduction.[29] Additional evidence of symptomatic improvement with twice daily IND/GLY (27.5/15.6 µg) is reflected in significant improvement in TDI scores at 12 weeks compared with placebo, IND (27.5 µg), and GLY (15.6 µg) treatment groups (1.64, 0.78, and 0.73 Unit improvements, respectively, $P < 0.001$ for all comparisons).[29]

Rescue Medication Rescue medication use was significantly reduced with twice daily IND/GLY

Figure 5: Twice Daily Indacaterol/Glycopyrrolate (27.5/15.6 µg) FDC: Lung Function (FLIGHT1 and FLIGHT2)[29]



*$P < 0.001$; IND/GLY FDC vs comparator

(27.5/15.6 µg) vs placebo over the 12 week study (mean daily puffs reduced by 1.2 vs placebo).

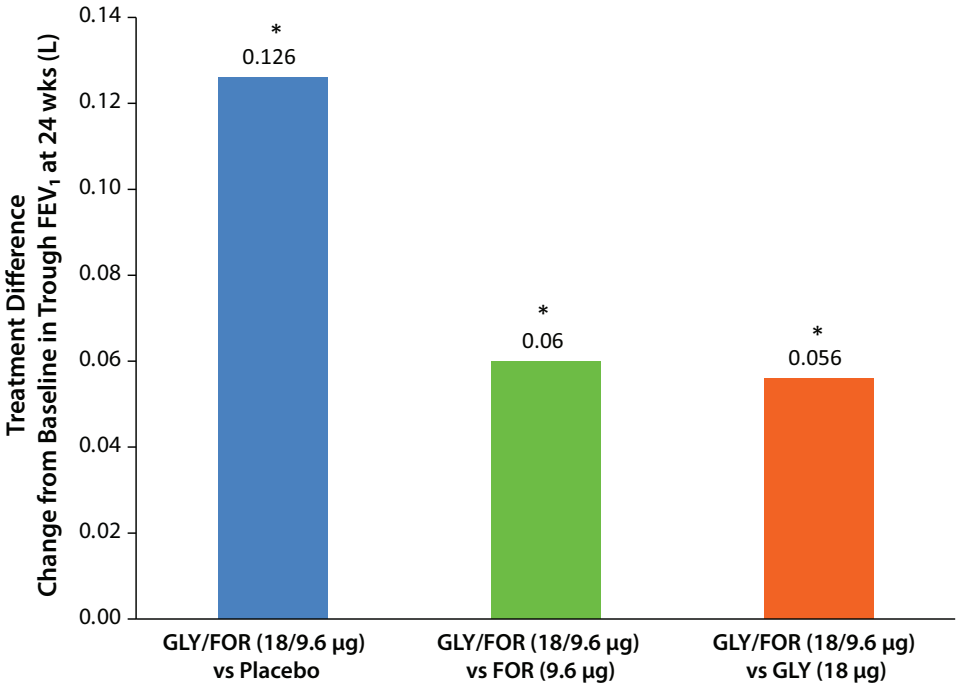
In a post-hoc subgroup analysis of FLIGHT1 and FLIGHT2, Ayers et al. recently reported that improvement in lung function, dyspnea, and health status associated with twice daily IND/GLY (27.5/15.6 µg) vs placebo and monocomponents is independent of prior maintenance therapy before study entry (LAMA, LABA, or LABA/ICS).[30]

Safety and Tolerability Pooled safety analysis from FLIGHT1 and FLIGHT2 indicated that the incidence of AEs was similar across treatment groups: 44%, 38%, 42% and 43% of patients in the IND/GLY, IND, GLY, and placebo groups, respectively, had at least one AE.[29] COPD worsening was the most commonly reported AE, ranging from 15.2% of patients treated with twice daily IND/GLY (27.5/15.6 µg) to 20.1% of patients in the placebo group. FLIGHT3 was a 52-week safety and tolerability study that included twice daily IND/GLY (27.5/15.6 µg), IND/GLY (27.5/31.2 µg), and IND (75 µg) treatment arms; the incidence of AEs was 68.1%, 69.6%, and 67.5%, respectively.[31] Ferguson et al recently reported the results of a subgroup analysis of FLIGHT3; specifically looking at the safety and tolerability of twice daily IND/GLY in the subgroup of 265 US participating patients with moderate-to-severe COPD.[32] In this subgroup, incidence of AEs and serious AEs was similar across treatment groups. Cardio- and cerebrovascular (CCV) events were reported in 5.3%, 5.4%, and 1.3% of patients in the IND/GLY (27.5/15.6 µg), IND/GLY (27.5/31.2 µg), and IND (75 µg) treatment arms, respectively.[32] The incidence of MACE and/or deaths was low across treatment groups; 2 events were reported in each of the IND/GLY treatment groups (27.5/15.6 µg and 27.5/31.2 µg), and none were reported in the group treated with IND (75 µg).[32]

GLYCOPYRROLATE/FORMOTEROL

Glycopyrrolate/formoterol (GLY/FOR) is a twice daily FDC bronchodilator recently approved by the US FDA for maintenance treatment of

Figure 6: Twice Daily Glycopyrrolate/Formoterol (18/9.6 µg) FDC: Lung Function (PINNACLE-1 and PINNACLE-2, Pooled Analysis)[35]



*$P < 0.0001$; GLY/FOR vs monocomponents, and placebo

patients with COPD.[33] GLY/FOR is delivered by pressurized metered dose inhaler; two inhalations result in GLY/FOR (18/9.6 µg) per dose. PINNACLE-1 and PINNACLE-2 were similar randomized, double-blind, placebo-controlled, parallel group, 24-week, phase 3 studies in which patients with moderate to very severe COPD were randomized to treatment with twice daily GLY/FOR (18/9.6 µg), GLY (18 µg), FOR (9.6 µg), or placebo.[34] PINNACLE-1 also included an open-label once daily TIO (18 µg) treatment arm. The primary endpoint was change from baseline in trough FEV_1 at 24 weeks.[34] A total of 3699 patients were randomized in the two studies.

Lung Function

Treatment with GLY/FOR (18/9.6 µg) resulted in significant improvement in trough FEV_1 at 24 weeks compared with monocomponents and placebo **(Figure 6).**[35]

In a post-hoc analysis of PINNACLE-1 and PINNACLE-2, Martinez et al. reported that the benefits in lung function associated with GLY/FOR (18/9.6 µg) FDC vs monotherapies and placebo extend to patients categorized as GOLD A or GOLD B.[35]

Table 4: Glycopyrrolate/Formoterol FDC: Pooled Analysis PINNACLE-1 and PINNACLE-2[35]

Endpoint	GLY/FOR (18/9.6 µg) vs Placebo	GLY/FOR (18/9.6 µg) vs FOR (9.6 µg)	GLY/FOR (18/9.6 µg) vs GLY (18 µg)
SGRQ Total Score (treatment difference, change from baseline at 24 weeks)	-2.13 $P = 0.005$	-0.64 $P = 0.283$	-1.56 $P = 0.009$
Daily Rescue Medication (treatment difference, puffs/day over 24 weeks)	-1.06 puffs/day $P < 0.0001$	-0.15 puffs/day $P = 0.124$	-0.42 puffs/day $P < 0.0001$

HRQL and Rescue Medication Treatment with twice daily GLY/FOR (18/9.6 µg) FDC was associated with improvement in SGRQ total score at 24 weeks and rescue medication use compared with placebo and GLY (18 µg) monotherapy, but not with FOR (9.6 µg) monotherapy **(Table 4)**.

Safety and Tolerability The safety profile of twice daily GLY/FOR (18/9.6 µg) FDC in the PINNACLE-1 and PINNACLE-2 studies was similar to the monocomponents, open-label TIO, and placebo, with 60% of patients in the GLY/FOR treatment group with at least one AE compared with 56%, 57%, 58%, and 63% in the GLY, FOR, placebo and TIO groups, respectively.[36] PINNACLE-3 was a 28-week extension of PINNACLE-1 and PINNACLE-2, designed to evaluate the long-term safety and tolerability of twice daily GLY/FOR (18/9.6 µg) FDC relative to GLY (18 µg), FOR (9.6 µg), and open-label once daily TIO (18 µg).[37] Of the 3,274 patients randomized to active treatment in PINNACLE-1 and PINNACLE-2, 893 continued into PINNACLE-3. Over a total of 52 weeks, incidence of AEs was similar across treatment groups, with nasopharyngitis and cough the most frequently reported events, ranging from 4.3% to 6.8% and 3.4 to 4.7% of patients respectively.[37] In patients treated with twice daily GLY/FOR (18/9.6 µg), 7.8% of patients discontinued due to AEs compared with 7.2% for GLY (18 µg), 6.0% in the FOR (9.6 µg) treatment group, and 6.2% of patients who received TIO (18 µg).[37]

Martinez FJ, et al. recently reported the results of a 24-hour Holter monitoring sub-study of PINNACLE-2.[38] In a sub-group of patients from this trial, continuous 12-lead electrocardiogram was conducted over a 24-hour period at baseline and at Week 4 following treatment randomization. The primary endpoint was the change from baseline to Week 4 in mean heart rate over 24 hours. A total of 585 patients were included in this monitoring study.[38] The Week 4 changes from baseline in 24-hour mean heart rate were very small in all subgroups: -0.5 beats/min in the GLY/FOR treatment group, -0.1 in patients treated with FOR, -1.1 with GLY, and 0.2 in the placebo treatment group. These changes along with 24-hour mean, maximum, minimum, daytime and nighttime heart rates were similar across treatment groups and not considered clinically significant.[38]

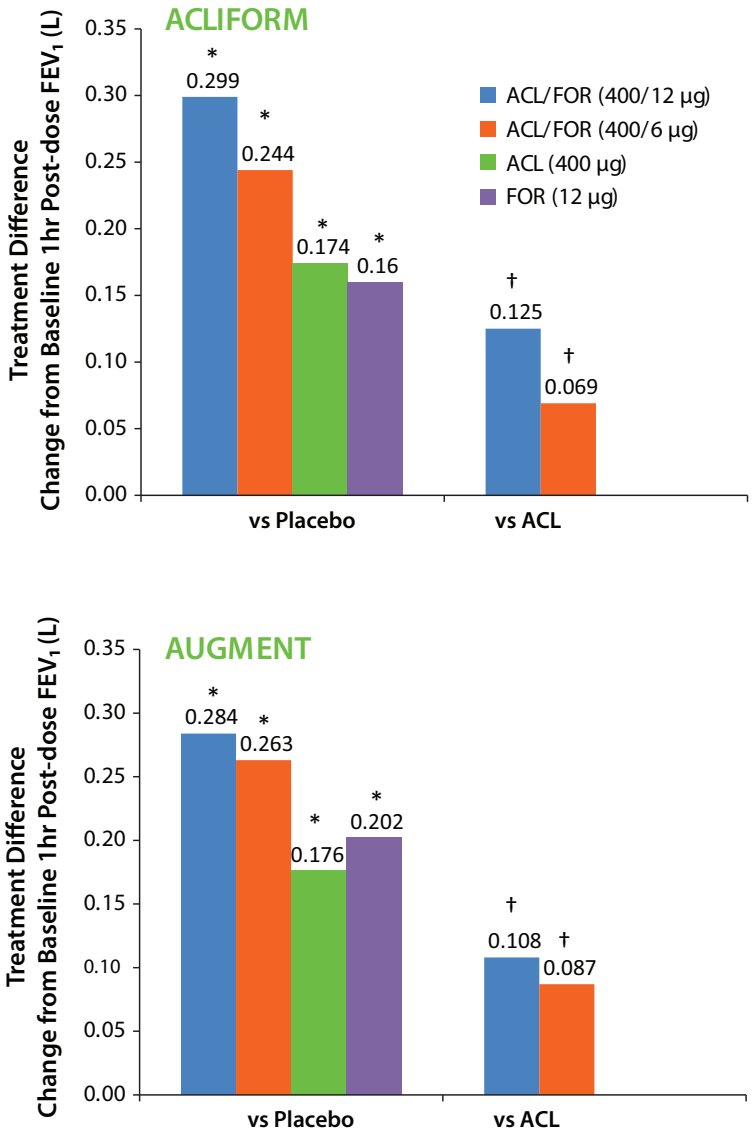
ACLIDINIUM/FORMOTEROL

Aclidinium/formoterol (ACL/FOR) FDC is approved in Europe as a twice daily inhaled maintenance treatment for patients with COPD delivered by dry powder inhaler (400/12 µg per dose).[39] ACL/FOR FDC has ***not*** been approved in the United States as of this writing (July 2016), therefore it is important to note that the studies described here relate only to the European approval of this long-acting bronchodilator combination. Two phase 3, double-blind, randomized, parallel-group, active and placebo-controlled studies have been conducted (ACLIFORM and AUGMENT) evaluating the safety and efficacy of the ACL/FOR FDC in patients with moderate-to-severe COPD.[40,41] Patients with moderate-to-severe COPD were randomized to treatment with ACL/FOR (400/12 µg), ACL/FOR (400/6 µg), ACL (400 µg), FOR (12 µg), or placebo. Co-primary endpoints in both studies were the change from baseline at Week 24 in 1-hour morning post-dose FEV_1 vs ACL (400 µg) and morning trough FEV_1 vs FOR (12 µg). Patients randomized include 1729 in ACLIFORM and 1692 in the AUGMENT study.

Lung Function In both studies, treatment with ACL/FOR FDC (400/12 µg and 400/6 µg) was associated with significant improvement in post-dose FEV_1 at 24 weeks compared with placebo and ACL **(Figure 7)**.[40,41] Significant

benefits were also observed for the ACL/FOR FDC in trough FEV_1 at Week 24 compared with placebo and FOR in both studies.

Figure 7: Aclidinium/formoterol FDC: Lung Function (ACLIFORM and AUGMENT)[40,41]



t*$P < 0.0001$ vs placebo; †$P < 0.05$ vs ACL

Dyspnea and Exacerbations

Bateman et al reported the results of a pooled analysis of symptoms and exacerbations from the ACLIFORM and AUGMENT studies, with a focus on the approved dose of ACL/FOR (400/12 µg) and associated monotherapies.[42] Treatment with ACL/FOR (400/12 µg) resulted in significant improvement in TDI focal scores at 24 weeks compared with placebo and monotherapies ($P < 0.05$, all comparisons).[42] Treatment with ACL/FOR (400/12 µg) was associated with significantly reduced rate of moderate or severe exacerbations compared with placebo (RR 0.71; 0.51-0.98, $P < 0.05$), but not compared with monocomponents.[42]

Composite Endpoint-Clinically Important Deterioration

In a post hoc pooled analysis of the ACLIFORM and AUGMENT studies, Singh et al. evaluated twice daily treatment with ACL/FOR (400/12 µg) on a composite endpoint of clinically important deterioration (CID) compared with monocomponents and placebo. For this analysis, CID was defined as 1 or more of the following: ≥ 100 mL change from baseline in 1 hour pre-dose (trough) FEV_1, ≤ 1 unit change from baseline in

TDI, ≥ 4 unit change from baseline in SGRQ, and occurrence of moderate/severe exacerbations.[43] Over the 24 week study, 57.8% of patients in the ACL/FOR (400/12 µg) had ≥ 1 CID compared with 63.9%, 65.5%, and 74.9% of patients in the ACL (400 µg), FOR (12 µg), and placebo groups, respectively ($P < 0.001$ vs placebo; $P < 0.05$ vs ACL, FOR).[43]

Safety and Tolerability Both doses of ACL/FOR were well tolerated in the ACLIFORM and AUGMENT studies, and the incidence of AEs was similar across treatment groups. Nasopharyngitis, cough and COPD exacerbation were the most frequently cited AEs.[40,41] AEs leading to discontinuation were reported in 6.3% of patients in the ACL/FOR (400/12 µg) treatment group and in 6.6% of those treated with ACL/FOR (400/6 µg) compared with 6.3%, 4.7%, and 4.2% of patients in the placebo, ACL (400 µg), and FOR (12 µg) treatment groups.[41]

As noted previously, ACLIFORM and AUGMENT were predominantly non-US studies, and the development of ACL/FOR FDC for approval in the United States is currently ongoing.[44]

Discussion

COPD treatment options continue to expand with an increasing number of inhaled LAMA/LABA FDCs approved for this patient population. As reviewed here, the approvals of these agents to date are supported by safety and efficacy data from large phase 3 trials **(Table 5, summary of efficacy outcomes)**. In the absence of direct head-to-head comparisons of LAMA/LABA FDCs, caution must be exercised in drawing comparisons between studies of these agents. There may be differences between studies in patient populations, inclusion/exclusion criteria, study designs, study duration, endpoints, methods and statistical analyses that make comparisons among studies difficult. Comparator studies are underway between certain LAMA/LABA products, but have yet to be completed or reported. In addition, studies are underway evaluating the effects of certain LAMA/LABA FDC to their monotherapies and to other FDC treatment options, including LABA/ICS and to triple therapy (LAMA/LABA/ICS), focusing on exacerbation frequency and severity.

A recent network meta-analysis reviewed the efficacy and safety of LAMA/LABA FDCs and identified 23 relevant trials with a total of 27,172 patients.[45] This analysis indicated that ***overall***, inhaled LAMA/LABA FDCs were associated with improvement over placebo in lung function (trough FEV_1 increase, mean improvement 201 to 243 mL), SGRQ (-4.1 mean difference), TDI (+ 1.21 mean difference), and reduction in moderate-to-severe exacerbations (HR = 0.66; 95% CI 0.57-0.77).[45] Compared with monotherapies, inhaled LAMA/LABA FDCs were associated with greater improvement in lung function parameters, SGRQ, and TDI. LAMA/LABA FDCs were associated with fewer moderate-to-severe exacerbations compared with placebo (HR 0.66; 95% CI 0.57-0.77) and LABAs (HR 0.82; 95% CI 0.73-0.93), but not compared with LAMAs (HR 0.92; 95% CI 0.84-1.00).[45] Statistically significant differences were not detected between LAMA/LABA FDCs, LAMAs, LABAs or placebo with regard to severe exacerbations. In addition, no significant differences were apparent for all comparators in mortality, serious AEs, or dropouts due to AEs according to this analysis.[45]

According to current GOLD guidelines, LAMA/LABA FDCs are treatment options for patients with COPD meeting criteria for GOLD groups B, C, or D as alternatives to LAMA or LABA monotherapy, or ICS + LABA or LAMA depending on the GOLD group.[3] In recent years, the place for ICS in patients with COPD has been a topic of discussion and debate. According to some studies, ICS may be inappropriately prescribed for some patients with COPD, such as those categorized as GOLD A and B[46,47] While ICS, particularly in combination with LABAs, have an important role in the management of COPD, recent studies have investigated step-down of ICS and the impact on exacerbations. OPTIMO was a prospective study to evaluate whether withdrawal of ICS in patients with COPD and low risk of exacerbation led to deterioration in lung function, symptoms, and increased frequency of exacerbations.[48] This real-life study included 914 patients with FEV_1 > 50% predicted, less than 2 exacerbations per year, and on maintenance therapy with bronchodilators and ICS. Of the patients who completed the 6 month study, 59% continued treatment with LABA/ICS and for 41% of patients, ICS was withdrawn. At the end of 6 months, FEV_1 and COPD Assessment Test scores did not change from baseline and there were no between group differences. Seventy-one percent of patients who continued with ICS were exacerbation free at 6 months compared with 74% of those for whom ICS were withdrawn (P = 0.347).[48] The WISDOM trial explored

Table 5: Summary of LAMA/LABA FDC Efficacy Outcomes

Treatment	Improvement in Lung Function (FEV_1 AUC and/or Trough FEV_1)			Improvement in Dyspnea (Transition Dyspnea Index)			Improvement in HRQL (St. George's Respiratory Questionnaire)		
	vs. Pbo	vs. Mono	vs. Active comp.	vs. Pbo	vs. Mono	vs. Active comp.	vs. Pbo	vs. Mono	vs. Active comp.
UMEC/VI FDC (62.5/25 µg) Once Daily									
Donohue et al.[9] 24 wks	↑	↑		↑	↔		↑	↔	
Decramer et al.[10] 24 wks		↑	↑		↔	↔		↔	↔
Maleki-Yazdi et al.[11] 24 wks			↑						↑
TIO/OLO FDC (5/5 µg) Once Daily									
Singh et al.[15] (OTEMTO 1, 2) 12 wks	↑	↑		↑	↑		↑	↑	
Buhl et al.[16] (TONADO-1, -2) 52 wks		↑			↑			↑	
IND/GLY FDC (110/50 µg) Once Daily									
Rodrigo et al.[26] (Review, 5 trials)	↑	↑	↑	↑	↑	↑	↑	↑	↑
IND/GLY FDC (27.5/15.6 µg) Twice Daily									
Mahler et al.[29] (FLIGHT 1, 2) 12 wks	↑	↑		↑	↑		↑	↑	
GLY/FOR FDC (18/9.6 µg) Twice Daily									
Martinez et al.[35] (PINNACLE-1, -2) 24 wks	↑	↑		↑	↑ (vs GLY)		↑	↑ (vs GLY)	
ACL/FOR FDC (400/12 µg) Twice daily									
Bateman et al.[42] (ACLIFORM, AUGMENT) 24 wks	↑	↑		↑	↑		↑	↔	

Pbo: placebo; Mono: monocomponents; Comp: comparator; ↑: statistically significant improvement; ↔: no significant difference

withdrawal of ICS in patients treated with two long-acting bronchodilators.[49] In this 12-month, double-blind, parallel-group study, 2485 patients with severe or very severe COPD and at least one exacerbation in 12 months before screening were stabilized on tiotropium, salmeterol and fluticasone monotherapies for 6 weeks and then randomized to continue this treatment or continue on tiotropium and salmeterol and to step down fluticasone to zero. The primary endpoint was time to first moderate or severe exacerbation. The hazard ratio for first moderate or severe exacerbation with ICS step-down was 1.06 (95% CI 0.94-1.19) compared with continuation of triple therapy.[49] At study Week 18 and at Week 52, trough FEV_1 reduction from baseline was significantly greater in the ICS step-down group compared with those who continued on triple therapy (treatment differences 38 mL and 43 mL, at weeks 18 and 52, respectively).[49] Additional studies are needed to inform individualized treatment decisions for patients with COPD at low risk for exacerbations regarding when and if step-down from ICS is appropriate. Ongoing studies of triple therapy (LABA + LAMA + ICS) include LAMA/LABA FDC treatment arms, which may provide additional data as to the role of LAMA/LABA FDCs in ICS-step down.[50,51]

Following are three patient case scenarios in which a LAMA/LABA FDC would be a reasonable treatment option. Onset of action, dosing frequency (once vs twice daily), potential side effects/drug-drug interactions, and inhalation devices (pressurized metered dose inhaler, soft mist inhaler, or dry powder inhaler) are among the considerations for individualized treatment decisions with LAMA/LABA FDCs in patients with COPD. Patients and their needs may change over time and routine evaluation of inhalation devices is important to ensure optimal medication delivery. Guidelines and treatment recommendations will no doubt evolve in the coming years with the availability of additional data from ongoing clinical trials, and the place for inhaled LAMA/LABA FDCs in the COPD treatment paradigm may change accordingly.

ASK THE EXPERTS!

Visit **www.PILOTforIPF.org/respirology** for an opportunity to ask the authors questions or to read questions from other learners. The authors will post answers every 2 weeks. Additional free online CME, downloadable slides, and resources are also available to pulmonologists, radiologists, and others who manage patients with pulmonary disease.

Case Scenarios: A Patient Newly Diagnosed with COPD

PRESENTATION

- 47-year-old female
- 33-year smoking history, still smoking
- Works for a professional cleaning service
- Increasing dyspnea over the past year (patient attributes this to getting older and putting on weight)
- Productive cough most mornings

HISTORY

- No comorbidities
- No current medications
- Bad case of bronchitis last winter—no treatment; not hospitalized
- Never been on medical therapy for respiratory symptoms

EXAM AND EVALUATION

- 5'5", 156 lbs
- Vitals normal
- Labs normal
- CXR normal
- Worsening dyspnea; productive morning cough
- No wheezing or crackles; slightly prolonged expiration
- CAT score: 15
- FEV_1 74% predicted
- Diagnosis of COPD, GOLD B

PULMONARY FUNCTION TEST *(next page)*

PULMONARY FUNCTION TEST

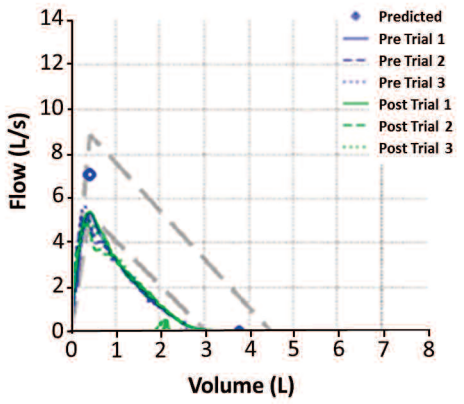
FVC (ex only) **Your FEV_1/Predicted: 74%**

Test Date	1/9/2016 10:59:17 AM	Interpretation	GOLD(2008)/Hardie	Value Selection	Best Value
Pos Date	1/9/2016 11:23:43 AM	Predicted	NHANES III	BTPS (IN/EX)	1.12/1.02
				User ID	820

			Pre					Post					
Parameter	Pred	LLN	Best	Trial 1	Trial 2	Trial 3	%Pred	Best	Trial 1	Trial 2	Trial 3	%Pred	%Chg
FVC [L]	3.79	3.06	3.39	3.39	3.36	3.34	89	3.36	3.30	3.36	3.27	88	-1
FVC_1 [L]	3.02	2.40	2.23*	2.22*	2.23*	2.21*	74	2.29*	2.29*	2.22*	2.27*	76	3
FEV_1/FVC	0.806	0.708	0.658*	0.654*	0.664*	0.663*	82	0.682*	0.694*	0.662*	0.696*	85	4
FEF25-75% [L/s]	2.94	1.63	1.19*	1.19*	1.26*	1.25*	41	1.44*	1.44*	1.27*	1.47*	49	21
PEF [L/s]	7.07	5.26	5.69	5.41	5.37	5.69	80	5.42	5.42	4.90*	5.02*	77	-5
FET [s]	–	–	14.0	14.0	14.1	13.3	–	13.3	13.3	13.4	12.1	–	-5

Session Quality	Pre	A [FEV_1 Var=0.01L (0.6%); FVC Var=0.03L (0.8%)]
	Post	A [FEV_1 Var=0.02L (0.7%); FVC Var=0.06L (1.7%)]
System Interpretation	Pre	Moderate Obstruction
	Post	Moderate Obstruction

***Indicatates value outside normal range or significant post change.**



TREATMENT SELECTION

A newly diagnosed patient has several treatment options. This person has moderate COPD with chronic symptoms (cough and dyspnea). She continues to smoke. She has also had an exacerbation in the previous year. Because of her chronic symptoms and prior exacerbation, she should be on more than just a PRN short-acting bronchodilator. In addition to smoking cessation counseling and therapy, the therapeutic options thus include:

- LABA
- LAMA
- LAMA/LABA

All of these therapies are reasonable options for this patient. The precise therapy chosen may depend on a number of factors, including how well the patient may be able to deal with different delivery devices, insurance coverage, etc. Going to a LAMA/LABA FDC is a reasonable option, if the goal is to attempt to maximize the patient's lung function. This patient would not be a candidate for an ICS-containing medication (either alone or in combination) at this point.

Patient with COPD and Hypertension and Heart Disease

PRESENTATION

- 52-year-old female
- 30-year smoker, stopped 15 years ago
- Diagnosed with COPD 3 years ago
- History of hypertension (15 years) and heart disease
- Increasing dyspnea and cough over the last 6 months

HISTORY

- Hypertension (15 years)
- COPD exacerbation last year
  - Hospitalized, treated with IV antibiotics and steroids
  - Sent home on LAMA (same treatment prior to hospitalization)
- Myocardial infarction following the exacerbation
- Recently seen by cardiologist
  - Stable, no angina

EXAM AND EVALUATION

- 5'3", 127 lbs
- Blood pressure slightly elevated (137/92)
- CXR normal
- No wheezing on examination
- CAT score = 22
- Current medications
  - LAMA
  - Beta blocker; statin
- FEV_1 52% predicted
- GOLD D

PULMONARY FUNCTION TEST *(next page)*

PULMONARY FUNCTION TEST

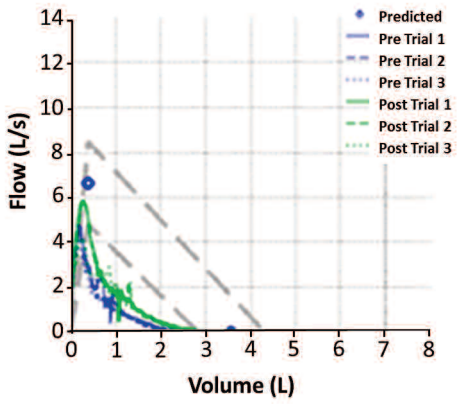
FVC (ex only) **Your FEV_1/Predicted: 52%**

Test Date	1/23/2016 12:09:56 PM	Interpretation	GOLD(2008)/Hardie	Value Selection	Best Value
Pos Date	1/23/2016 12:32:42 PM	Predicted	NHANES III	BTPS (IN/EX)	1.12/1.02
				User ID	820

			Pre					Post					
Parameter	Pred	LLN	Best	Trial 1	Trial 2	Trial 3	%Pred	Best	Trial 1	Trial 2	Trial 3	%Pred	%Chg
FVC [L]	3.57	2.83	2.72*	2.72*	2.68*	2.55*	76	3.08	3.08	3.05	3.07	86	13*
FVC_1 [L]	2.76	2.14	1.43*	1.43*	1.38*	1.32*	52	1.74*	1.74*	1.73*	1.71*	63	22*
FEV_1/FVC	0.780	0.682	0.524*	0.524*	0.516*	0.517*	67	0.566*	0.566*	0.566*	0.556*	73	8
FEF25-75% [L/s]	2.47	1.15	0.51*	0.51*	0.40*	0.48*	21	0.70*	0.70*	0.70*	0.62*	28	39
PEF [L/s]	6.63	4.80	4.80	4.80	4.56*	4.06*	72	5.91	5.91	5.80	4.21*	89	23
FET [s]	–	–	15.2	15.2	18.4	14.6	–	12.8	12.8	12.5	15.4	–	-15

Session Quality	Pre	A [FEV_1 Var=0.05L (3.2%); FVC Var=0.05L (1.7%)]
	Post	A [FEV_1 Var=0.02L (0.9%); FVC Var=0.01L (0.5%)]
System Interpretation	Pre	Moderate Obstruction
	Post	Moderate Obstruction
Overall Syst. Interpret.	Significant pre - post change	

***Indicatates value outside normal range or significant post change.**



TREATMENT SELECTION

This patient is currently on a LAMA, but based on her elevated CAT score, exacerbation history, and bronchodilator response on spirometry, her therapy should be advanced. Reasonable options include:

- Change from LAMA to LAMA/LABA FDC
- Add LABA/ICS FDC to LAMA

Stepping up therapy is done for a number of reasons. Typically, this follows an exacerbation event or an increase in symptomatology. In this case, the patient would likely benefit from additional pharmacologic therapy. She should also be evaluated and referred to a pulmonary rehabilitation program.

The rationale for changing to a LAMA/LABA FDC is that she might benefit from additional bronchodilation. Another advantage is that she would not be on an ICS, which may increase the risk of pneumonia. A disadvantage is that she would have to change inhalers. This patient has cardiovascular comorbidities; however studies have not identified significant cardiovascular AEs with LAMA/LABA FDC treatment compared with monocomponents or active controls.

The rationale for adding a LABA/ICS FDC is that she might benefit from both additional bronchodilation and an anti-inflammatory agent. This might be the case if she has an asthmatic component to her disease. She would need an additional inhaler, but an LABA/ICS FDC can be added to her regimen in either a once daily or twice daily formulation. A potential disadvantage is that the use of ICS increases the risk of pneumonia.

Stepping Down from Triple Therapy

PRESENTATION

- 64-year-old male
- Cigarette smoker
  - 1.5 packs for 35 years
  - Quit smoking when he started having respiratory problems; occasional cheating, but had largely quit
- Relatively active; initially had cough, sputum, shortness of breath with activity such as golf or yard work
- Diagnosed with COPD 8 years ago (in 2007)

HISTORY, 2007

- 6'2", 200 lbs
- Vitals normal
- Mild increase in AP diameter
- Reduced breath sounds; occasional rhonchi without crackles, wheezes, or accessory muscle usage
- No lower extremity edema
- CXR minimal hyperinflation; otherwise normal
- FEV_1 46% predicted
- Mild hyperinflation with TLC 110% predicted, RV 130% predicted
- Diffusion capacity 68% predicted
- Did not require oxygen; O_2 saturation 93-94%
- Comorbidities
  - Hypertension, hypercholesterolemia, arthritis
  - Medications: ACE inhibitor, diuretic, statin

INITIAL COPD TREATMENT, 2007

- LAMA, once daily

HISTORY CONTINUED

- COPD outpatient exacerbation, 2008 (responded well to antibiotics and steroids)
- Severe COPD exacerbation in 2009
  - Severe symptoms; hypoxemia
  - Hospitalized for 4 days
  - Did not require intubation, ventilatory support or BiPAP
  - Aggressive nebulized therapy; IV antibiotics and steroids
  - Gradually improved
- Treatment adjustment at discharge
  - LAMA + LABA + ICS
  - Went through pulmonary rehabilitation and did well
  - Variably compliant with his exercise program (better during summer, less so in winter)
  - Moderate COPD exacerbation, 2011
- Short course of antibiotics and steroids as an outpatient
  - **Stable for 3 years** (LAMA + LABA + ICS; PRN albuterol inhaler)
  - No further exacerbations or problems
  - Retired and now goes to Florida for the winter

HISTORY, 2015

- Complains of difficulty with his delivery device for LAMA (arthritis in his hands makes it difficult to remove medication capsules from blister packaging before placing the capsules in the inhalation device)
- He asked if there are other options that might be easier to use
- Switched to a different inhaler with the same LAMA (inhalation spray; no need to remove capsules from bister packaging prior to use)
- Continued with LABA + ICS twice daily
- Trial for 4-6 weeks
- Good transition with the new inhaler; the device was much easier to use
- He inquires if his other medicine (LABA + ICS) can be delivered using the same inhaler

TREATMENT SELECTION *(next page)*

AN UPDATE ON
Fixed-Dose LAMA/LABA Inhalers in COPD

TREATMENT SELECTION

In 2007, this patient was diagnosed with COPD GOLD D. With the options of starting either LABA/ICS or LAMA at that time, the decision was made to start LAMA monotherapy based on lack of exacerbations and the need for improvement in airflows and symptoms control.

In 2009, an additional intervention was required due to increased symptoms and a severe COPD exacerbation requiring hospitalization. Beyond education and rehabilitation, the addition of a LABA/ICS was indicated to further reduce the risk of COPD exacerbations and readmissions.

With changes in mental cognition, arthritis and various medical conditions that may occur over time, selection of an inhaler delivery system that is usable by a patient is critical. In this patient case, the switch in inhalation device allowed for the patient to obtain the same effective medication in a manner that he could perform correctly without added assistance.

The goal of tailoring therapy to a patient's individual needs for both optimal improvement in airflows and function along with prevention of future risks, especially exacerbations, need to be continuously assessed. In addition, the appropriateness of a particular delivery system for a patient and the convenience and potential cost savings of using a fixed dose combination should be considered as part of decision making in patient management. The value perceived by the patient in using an easier delivery system based on his arthritis and the lower COPD exacerbation risk associated with effective control for over 7 years in this patient raised the possibility of reducing therapy by eliminating ICS therapy. The key question at that time was the risk of ICS withdrawal in a GOLD D COPD patient well controlled on triple therapy. If feasible, this would allow for the use of a single inhaler as a LAMA/LABA fixed dose combination using the same delivery system.

Review of the OPTIMO and WISDOM trial data suggest that ICS step-down or withdrawal may be appropriate in select patients on triple therapy. Certainly if triple therapy was never truly indicated for a patient, ICS therapy may be withdrawn as in the OPTIMO trials. In this patient's case, he does have appropriate indications for the use of ICS, but the lack of exacerbations for 7 years on therapy and the desire for a single inhaler with a desired delivery system raised the possibility, as supported by the WISDOM data. After careful discussion of the risks and benefits with the patient, he concurred that he would like to make the change to LAMA/LABA FDC, with close observation for deterioration.

To date he has done and continues to do well with LAMA/LABA FDC therapy.

References

1. World Health Organization. http://www.who.int/respiratory/copd/burden/en/. Accessed July 2016.

2. American Lung Association. http://www.lung.org/lung-health-and-diseases/lung-disease-lookup/copd/learn-about-copd/how-serious-is-copd.html. Accessed July 2016.

3. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management and Prevention. Updated 2015. http://www.goldcopd.it/materiale/2015/GOLD_Pocket_2015.pdf. Accessed July 2016.

4. Spina D. Pharmacology of novel treatments for COPD: are fixed dose combination LABA/LAMA synergistic? *Eur Clin Respir J*. 2015;2:26634.

5. Singh D. New combination bronchodilators for chronic obstructive pulmonary disease: current evidence and future perspectives. *Br J Clin Pharmacol*. 2015;79:695-708.

6. FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name. Accessed July 2016.

7. European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. Accessed July 2015.

8. FDA. Umeclidinium and vilanterol inhalation powder. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203975s003lbl.pdf. Accessed July 2016.

9. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol62.5/25 mcg in COPD. *Respir Med*. 2013;107(10):1538-46.

10. Decramer M, Anzueto A, Kerwin E, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. *Lancet Respir Med.* 2014;2:472-486.

11. Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umeclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease: results of a 24-week, randomized, controlled trial. *Respir Med*. 2014;108:1752-1760.

12. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, Riley JH. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. *Ther Adv Respir Dis*. 2014;8:169-181.

13. Naccarelli G, Finkle J, Chopra B, Brooks J, Harris S, Church A. Cardiovascular safety of umeclidinium/vilanterol in COPD: results from eight randomized clinical trials. *Am J Respir Crit Care Med*. 2014;189:A3766.

14. FDA. Tiotropium and olodaterol inhalation spray. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206756s006lbl.pdf. Accessed July 2016.

15. Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med*. 2015;109:1312-1319.

16. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J.* 2015;45:969-979.

17. Ferguson GT, Flezar M, Korn S, Korducki L, Gronke L, Abrahams R, Buhl R. Efficacy of tiotropium + olodaterol in patients with chronic obstructive pulmonary disease by initial disease severity and treatment intensity: a post-hoc analysis. *Adv Ther.* 2015;32:523-536.

18. Singh D, Gaga M, Schmidt O, Bjermer L, Gronke L, Vos F, Ferguson GT. Effects of tiotropium + olodaterol versus tiotropium or placebo by COPD disease severity and previous treatment history in the OTEMTO studies. Respir Res. 2016;17:73.

19. Cooper CB, et al. Analysis of rescue medication use over 1 year in patients receiving LAMA, LABA, or combination maintenance treatment for COPD in the TONADO® studies. *AJRCCM*. 2016;193:A6807.

20. Buhl R, McGarvey L, Korn S, et al. Benefits of tiotropium + olodaterol over tiotropium at delaying clinically significant events in patients with COPD classified as GOLD B. *AJRCCM*. 2016;193:A6779.

21. Derom E, et al. Effect of tiotropium + olodaterol therapy on COPD exacerbations in the TONADO® studies. *AJRCCM*. 2016;193:A6805.

22. Rossi A, Zanardi E, Poletti V, Cazzola M. Clinical role of dual bronchodilation with an indacaterol-glycopyrronium combination in the management of COPD: its impact on patient-related outcomes and quality of life. I*nt J Chron Obstruct Pulm Dis*. 2015;10:1383-1392.

23. FDA. Indacaterol and glycopyrrolate inhalation powder. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207930s000lbl.pdf. Accessed July 2016.

24. Banerji D, Mahler DA, Hanania NA. Efficacy and safety of LABA/LAMA fixed-dose combinations approved in the US for the management of COPD. *Expert Rev of Respir Med.* 2016;10:767-780.

25. Prakash A, Babu KS, Morjaria JB. Profile of inhaled glycopyrronium bromide as monotherapy and in fixed-dose combination with indacaterol maleate for the treatment of COPD. *Int J COPD*. 2015;10:111-123.

26. Rodrigo GJ, Plaza V. Efficacy and safety of a fixed-dose combination of indacaterol and glycopyrronium for the treatment of COPD. A systematic review. *CHEST*. 2014;146:309-317.

27. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med*. 2016;374:2222-2234.

28. Watz H, Mailander C. Baier M, Kirsten A. Effects of indacaterol/glycopyrronium (QVA149) on lung hyperinflation and physical activity in patients with moderate to severe COPD: a randomized, placebo-controlled, crossover study (The MOVE Study). *BMC Pulmonary Med*. 2016;16:95.

29. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: Efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192:1068-1079.

30. Ayers T, et al. Indacaterol/glycopyrrolate improves lung function, dyspnea and health status in symptomatic patients with COPD using prior LAMA, LABA or LABA/ICS: post-hoc analysis from pooled FLIGHT1 and FLIGHT2 Studies. *AJRCCM*. 2016;193:A6800.

31. Ferguson GT, Fowler Taylor A, Thach C, Wang Q, Schubert-Tennigkeit AA, Banerji D. QVA149 is safe and well tolerated in patients with moderate to severe COPD: FLIGHT3, a 52 week safety study. *AJRCCM*. 2015;192:A5762.

32. Ferguson GT, et al. Long-term safety and tolerability of indacaterol/glycopyrrolate in moderate-to-severe COPD patients from the US: a subgroup analysis from the FLIGHT3 study. *AJRCCM*. 2016;193:A6788.

33. FDA. Glycopyrrolate and formoterol fumarate inhalation aerosol. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208294s000lbl.pdf. Accessed July 2016.

34. Rabe K, Martinez F, Rodrigues-Roisin R, et al. PT003, a novel co-suspension MDI glycopyrronium/formoterol fixed dose combination is superior to monocomponents in patients with COPD. *Eur Respir J*. 2015;46(S59):LBA.

35. Martinez FJ, et al. Pooled analyses from PINNACLE-1 and -2: the novel LAMA/LABA co-suspension technology glycopyrrolate/formoterol fixed-dose combination delivered by MDI shows improvement versus monocomponents in patients with COPD. *AJRCCM*. 2016;193:A6782.

36. Ferguson GT, et al. Pooled analyses from PINNACLE-1 and -2: safety profile of the novel LAMA/LABA co-suspension technology fixed-dose combination (glycopyrrolate/formoterol) delivered by MDI, in patients with chronic obstructive pulmonary disease (COPD). *AJRCCM*. 2016;193:A6790.

37. Hanania N, et al Safety and efficacy of a novel LAMA/LABA co-suspension technology glycopyrrolate/formoterol fixed-dose combination delivered by MDI: results of a one-year extension study in patients with COPD (PINNACLE-3). *AJRCCM*. 2016;193:A6791.

38. Martinez FJ, et al. Cardiovascular safety profile of a novel LAMA/LABA co-suspension technology fixed-dose combination of glycopyrrolate/formoterol delivered by metered dose inhaler in patients with COPD: 24-hour holter monitoring study. *AJRCCM*. 2016;193:A6783.

39. EMA. Aclidinium formoterol inhalation powder. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003969/WC500178254.pdf. Accessed July 2016.

40. Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. 2014;14:178.

41. D'Urzo AD, Rennard SI, Kerwin EM, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res*. 2014;15:123.

42. Bateman ED, Chapman KR, Singh D, D'Urzo AD, Molins E, Leselbaum A, Gil EG. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res*. 2015;16:92.

43. Singh D, et al. Reduction in clinically important deterioration in chronic obstructive pulmonary disease in patients treated with aclidinium/formoterol combination. *AJRCCM*. 2016;193:A6771.

44. NCT02796677. AMPLIFY- D6571c00001 Duaklir USA Phase III Study. https://clinicaltrials.gov/ct2/show/NCT02796677. Accessed July 2016.

45. Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. *Thorax*. 2016;71:15-25.

46. Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J COPD*. 2015;10:2207-2217.

47. Kaplan AG. Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice. *Int J COPD*. 2015;10:2535-2548.

48. Rossi A, Guerriero M, Corrado A. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res*. 2014;15:77.

49. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *NEJM*. 2014;371:1285-1294.

50. NCT02164513. A study comparing the efficacy, safety and tolerability of fixed dose combination (FDC) of FF/UMEC/VI with the FDC of FF/VI and UMEC/VI; administered once-daily via a dry powder inhaler (DPI) in subjects with chronic obstructive pulmonary disease. https://clinicaltrials.gov/ct2/show/NCT02164513. Accessed July 2016.

51. NCT02465567. Study to assess the efficacy and safety of PT010 relative to PT003 and PT009 in subjects with moderate to very severe COPD (Ethos). https://clinicaltrials.gov/ct2/show/NCT02465567 Accessed July 2016.

Provided by
The France Foundation

ASK THE EXPERTS!

Visit www.PILOTforIPF.org/respirology
to ask the authors questions