If we are looking at the last advances in the therapy of COPD we can observe that the COPD pipeline consists of more than 200 products mainly bronchodilators and on second place anti-inflammatories. The competition is open and every research department of the pharmaceutical companies try to do his best. It’s not only a competition between drug classes it is also a competition of concepts where we can see in this moment some representatives in full position such as long acting muscarinic antagonists (LAMAs) or long acting β2-adrenoceptor agonists (LABAs), but also some new inhaled steroids, even if the role of inhaled steroid for chronic treatment remains controversial and largely unresolved. This new coming generations changed also the strategies and the GOLD board was obliged to take into account and to accept for the first time in 2014 the first fixed combination of LABAs and LAMAs as an efficient therapy. The experts recommend combining bronchodilators of different pharmacological classes to improve efficacy and decreasing the risk of side effects compared to increasing the dose of a single bronchodilator. It was a successive incoming of the new generations of combination of LABAs and LAMAs. A first indication remains the COPD patients not adequately controlled with monotherapy resulting in the development of an increasingly confusing variety of LAMA+LABA fixed-dose combinations (FDCs) and their respective generic clones.

Bronchodilators from the LABAs and LAMAs family are remaining the cornerstone of maintenance therapy for patients with moderate-to-severe COPD whose symptoms are not adequately controlled by short-acting bronchodilators alone. Bronchodilators from this two classes exert their effect by smooth-muscle relaxation, resulting in improved lung emptying, reduced thoracic gas volume and residual volume, as well as lessened dynamic hyperinflation and improved inspiratory capacity. The real progress are in other directions; after a decade with LABAs like formoterol, salmeterol, which requires twice-daily dosing surviving on the market for a long period, and more recently once-daily indacaterol, and the once-daily LAMA tiotropium where dominating therapeutic options in moderate-to-severe COPD. Studies have demonstrated that if these bronchodilators coming from different classes are used concurrently, there is further significant improvement in lung function and health-related quality of life measures, symptoms scores, rescue medication use and exercise capacity. Another step after was to develop the novel once-daily combinations of LABAs and LAMAs in one inhaler. These LAMAs and LABAs potentially offer greater convenience and compliance compared with the use of two separate inhalers. It was a family growing from one year to other if we are thinking to: glycopyrronium bromide/indacaterol maleate (QVA149 [Ultibro®]; Novartis International AG, Basel, Switzerland) (available in Australia, Japan, and Europe) and delivered via the Breezhaler®; umeclidinium bromide/vilanterol trifenatate (Anoro®; GlaxoSmithKline, London, UK) (available in Australia, USA, and Europe), delivered via the Ellipta®, tiotropium bromide/olodaterol (Spiolto®; Boehringer Ingelheim, Ingelheim, Germany) delivered with the Respimat® Soft Mist™ inhaler, and aclidinium bromide/formoterol (LAS40464; Almirall, Barcelona, Spain) delivered via the Genuair® inhaler (available in Europe). Each combination is delivered through a unique dry powder delivery device, making comparative assessments difficult. Until this moment looking to all the national and international guidelines the combination are recommended for:

- this extra bronchodilation provided in comparison to monotherapy (with or without inhaled corticosteroids) (ICS), in case of persistent symptoms with only LAMA or LABA
- the cases where the addition of ICS is declined or not tolerated or when the COPD is stable with an FEV1 > 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA
- symptomatic patients with stable COPD and FEV1 < 60% predicted (graded as a weak recommendation with moderate quality evidence to support its use)
There is still little evidence to determine the efficacy of FDC LABA/LAMA inhalers on exacerbation rates, but even so, the crucial role of these drugs has, in part, been helped by the fact that long-acting bronchodilators, and LAMAs (tiotropium one of them) in particular, have demonstrated: efficacy in preventing COPD exacerbations, a good safety record and might even decrease mortality14,15.

In one of the first issues 2015, of the European Respiratory Journal, a novel candidate of this drug combination principle is presented by BUHL et al.15 the olodaterol and tiotropium combination delivered via the Respimat Soft Mist inhaler. Olodaterol (Striverdi®) is a long-acting, inhaled, β2-adrenergic receptor agonist with a 24-hour bronchodilator profile. This LABA received its first global approval in 2013 for the long-term, once-daily as maintenance bronchodilator treatment of airflow obstruction in patients with COPD in Canada16.

It was approved by the FDA in July, 2014, for maintenance bronchodilator treatment in patients with COPD. Olodaterol is a long-acting beta2 agonist (LABA) that activates specific β2-adrenergic receptors on the surface of smooth muscle cells, which increases intracellular cAMP and smooth muscle relaxation. After, it has been approved in a number of European countries as a once-daily dose of 5 μg given through a Respimat® Soft Mist™ inhaler17.

A recent meta-analysis where 18 trials were identified (eight, olodaterol; ten, indacaterol) evaluating the efficacy of olodaterol and indacaterol in patients with COPD, concluded that both olodaterol and indacaterol had similar efficacy when compared under similar trial conditions18.

On the other part Tiotropium is a “veteran” of LAMAs. Tiotropium has been on the market for at least 15 years and is the first-line long-acting anticholinergic bronchodilator for maintenance therapy in COPD at the dose of 18 μg (delivered by Handi Haler and 5 μg delivered by Respimat Soft Mist inhaler)19.

Tiotropium is an established once-daily LAMA that improves lung function and several patient-orientated outcomes of COPD, and has also been suggested to moderate disease progression in milder forms of COPD20. Respimat® is a fine-mist inhaler delivering the medication independent of inspiratory effort and patient coordination21 Respimat® overcomes some of the limitations of pressurized metered dose inhalers (pMDI), dry powder inhalers, and nebulizers as it is portable, propellant-free, and does not need a spacer/holding chamber.

The new combination of both drugs where used in two replicate phase III trials aimed to assess the efficacy and safety of inhaled tiotropium + olodaterol FDC 5/5 μg or 2.5/5 μg delivered via the Respimat Soft Mist inhaler compared with their individual mono-components in patients with moderate-to-very-severe COPD (Global Initiative for Chronic Obstructive Lung Disease stage 2–4) over 52 weeks1,15.

The authors hypothesised that combination therapy with tiotropium + olodaterol FDC would provide improvements in lung function, health-related quality of life (St George’s Respiratory Questionnaire (SGRQ) total score at 24 weeks) and other COPD disease parameters compared to monotherapy with either component alone, and with a comparable safety profile15. Primary end points were forced expiratory volume in 1 s (FEV1) area under the curve from 0 to 3 h (AUC0–3) response, trough FEV1 response and St George’s Respiratory Questionnaire (SGRQ) total score at 24 weeks15. In total, 5162 patients (2624 in Study 1237.5 and 2538 in Study 1237.6) received treatment. Both FDCs significantly improved FEV1 AUC0–3 and trough FEV1 response versus the mono-components in both studies. Statistically significant improvements in SGRQ total score versus the mono-components were only seen for tiotropium + olodaterol FDC 5/5 μg15. Incidence of adverse events was comparable between the FDCs and the mono-components15.

The strong points of the study are: it’s a large one and of a good quality1. Other conclusions important for the future of all fixed combinations are coming from the results of this studies: Tiotropium/olodaterol Respimat® showed efficacy across all COPD stages with greatest lung function improvements over Spiriva® Respimat® in early stages of COPD22,23.

The new analyses suggest that tiotropium/olodaterol Respimat® may “help improving lung function from the time of diagnosis of COPD when patients are first beginning maintenance therapy” as the author prof. Buhl said. TOnado study as prof. Rabe also added « will ring a bell in the mind of the reader since it is mainly about increasing volume of air”. The limits also are: the lack of a placebo group as the authors mentioned, but probably inevitable, since for this patient group of symptomatic COPD patients it seems indeed inappropriate to deny the use of long-acting bronchodilator for 1 year. It exist another recent study24 where they had a placebo group but for only 6 weeks; it demonstrates a significant improvement in FEV1 AUC 0-24 response observed with tiotropium / olodaterol 5/5 mg and 2.5/5 mg versus placebo and monotherapies and a mean response of 0.280 L (p < 0.0001) versus placebo with tiotropium / olodaterol 5/5 mg. The limits of this study are also coming from the short duration of the study and the crossover design limiting the safety information. What is likely of more relevance in the Buhl study is the choice of endpoint, and the fact that exacerbations were not analysed, despite the size of the population and duration of the trial1.

An other possible contribution of the Buhl study is: like earlier studies on bronchodilators in COPD, the present trial confirmed the overuse of other treatments- almost 50% of patients were on inhaled corticosteroids despite the relatively mild disease severity of the population, and almost 10% were on xanthines1.
After this novel results of a new efficient combination we are facing the same questions valuable for all this representatives of LABA/LAMAs fixed combinations:

- for the treatment of mild disease and severe COPD we have to justify additional costs of LAMA/LABA combinations.
- what are the benefits on exacerbations rate and mortality on long term?
- what we really want to know is whether this drug combination (but also the other combinations) will affect (severe) exacerbations and hospitalisations, and ultimately death.
- large head-to-head comparisons among the new long-acting bronchodilators (LABA/LAMA) are required.

Perhaps some of the answers will come from the trial assessing the efficacy of FDC tiotropium and olodaterol on exacerbations and survival, DYNAGITO068 (NCT0 2296138), who has started recruiting patients from January 2015. This new combination as other FDC LABA/LAMA therapies are expected to become part of the pharmacological armamentarium in the management of COPD, confirming once again the improved efficacy and compliance on the COPD patients. It’s another window open for encouraging the practice of “personalized” medicine where choices are guided by patient preference to drug and device, as well as phenotypic features (eg, breathlessness, non-eosinophilic airway inflammation).

Disclosure
The authors report no conflicts of interest in this work.