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DRUG EVALUATION

Evaluating revefenacin as a therapeutic option for chronic obstructive pulmonary disease

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ABSTRACT

Introduction: In chronic obstructive pulmonary disease (COPD), inhaled long-acting antimuscarinic agents (LAMA) are effective maintenance therapies used across all severity stages of the disease. Most of them are administered via dry powder inhalers, but these devices require a potent inspiratory flow which cannot be effectively achieved by patients with advanced disease. In such patients, inhaled therapy via nebulization might be an option.

Areas covered: Revefenacin is a LAMA that was specifically formulated for once daily nebulization and which was authorized by the FDA as a maintenance therapy for COPD. In phase II and III clinical studies discussed in this review, revefenacin demonstrated its rapid onset of action and sustained effect on lung function on both a short- and long-term basis.

Expert opinion: Nebulized revefenacin with once daily use does not require any particular effort of administration and hence can be used by patients with severe airways obstruction or by those having milder cognitive deficits. Further studies are needed, however, to better document the long-term cardiovascular safety and its ability to reduce the exacerbation rate.

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Chronic obstructive pulmonary disease; inhaled therapies; long-acting antimuscarinic; nebulization; revefenacin; tiotropium

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease that is mainly related to smoking. Its prevalence is increasing worldwide despite sustained efforts to curb smoking rates, and this is due to the increase in outdoor and indoor air pollution and, unexpectedly, improved disease outcome as a result of regular use of various-inhaled therapies that can reduce chronic respiratory symptoms and improve survival. COPD is also associated with significant medical, economic, and societal burden, especially in the advanced stages.

Inhaled therapies are mostly used in the stable phase of the disease and mainly represented by bronchodilators, which are used across all stages of disease severity, whereas inhaled corticosteroid use is increasingly restricted to patients with COPD in whom eosinophilic inflammation is present in the airways and at systemic levels [1].

Inhaled bronchodilators that are recommended to be used on a regular basis in COPD are represented by long-acting β2 agonists and long-acting muscarinic agonists (LAMAs) and their combinations. Most of them are used in maintenance COPD therapy administered via various types of inhalation devices, such as metered dose inhalers or dry powder inhalers. Nebulization is another route of administration of inhaled therapy; however, in COPD, it is used in an acute setting rather than as maintenance therapy. Revefenacin (Yupelri®) is the newest inhaled LAMA developed for nebulization use in stable COPD therapy, which was approved in the USA for this therapeutic indication [2].

2. Market overview

LAMAs can be used as monotherapy in COPD with a lower disease burden, that is, less severe dyspnea, better quality of life, better lung function, and no or less severe disease exacerbations. Tiotropium bromide is the first LAMA approved in both the USA and EU for maintenance therapy in COPD. Tiotropium bromide demonstrated its therapeutic potential on both short- and long-term bases [3–5]. It was previously developed as capsules for daily inhalation route (delivering device, HandiHaler) and is currently marketed as a solution for inhalation delivered via a soft mist inhaler, called Respimat, with the same dosing schedule and comparable efficacy [6]. Subsequent LAMAs that became available for COPD were all formulated for dry powder inhalation and represented by aclidinium bromide, umeclidinium bromide, and glycopyrronium bromide, formulated for once or twice daily inhalations.

An ideal inhaled LAMA in COPD settings are that with few daily dosages, fast onset of action, and ability to achieve therapeutic concentrations in the small-caliber airways irrespective of the severity of airflow limitation. The characteristics of the inhalation device and patient's respiratory status greatly influence the efficacy of the active substance. Hence, a route of administration that is easy to master and provides the medication with no particular respiratory effort from the patient, such as nebulization, can be of significant advantage for the patients. Furthermore, the only inhaled antimuscarinic agent also formulated for nebulization use is ipratropium

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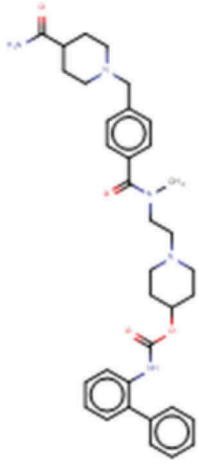
Box 1. Drug summary.

Drug name	Revefenacin
Phase	Launched
Indication	Chronic Obstructive Pulmonary Disease
Pharmacology description	Long-acting antimuscarinic drug
Route of administration	Inhaled (Nebulization)
Chemical structure	
Pivotal trial(s)	(1)

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bromide, which is a short-acting compound. This indicates that regular dosing requires four nebulizations daily, and this might not be convenient for the patient. Therefore, a LAMA that can be nebulized and dosed once daily or at least fewer times might increase the patient's adherence and indirectly the clinical efficacy of the treatment. Glycopyrrolate (Lonhala Magnair®) formulation for nebulization use twice daily is approved by the FDA for maintenance therapy in COPD [7]. Revefenacin (Yupelri®) is a LAMA formulated for nebulization, which was tested clinically as a regular therapy in patients with COPD and approved by the FDA as COPD therapy [2].

3. Introduction to the compound: chemistry and preclinical data

This compound was initially developed as TD-4208. Its chemical structure is biphenyl-2-ylcarbamic acid 1-(2- [8]ethyl)piperidin-4-yl ester [8,9]. Preclinical in vitro testing demonstrated that TD-4208 is a potent and selective M3 muscarinic receptor antagonist with high affinity and persistent inhibitory effect in the airways in whom low systemic absorption and nonsignificant extra respiratory effects have been reported [8,9]. The affinity, binding potency, and functional activity of TD-4208 were tested on type M1, M2, M3, M4, or M5 human recombinant muscarinic receptors expressed by whole-cell membranes or their portions. *In vitro* pharmacodynamic studies on smooth muscle cells in tracheal rings isolated from guinea pigs were also conducted. The binding constant (Ki) was found to be 0.42 for M1 receptors, 0.32 for M2 receptors, and 0.18 for M3 receptors. M3 binding selectivity was shown to be due to a longer dissociation half-life of the radiolabeled compound, which was 81 min for M3 receptors compared to 6.9 min for M2 receptors. Pharmacodynamics analysis demonstrated the inhibitory (bronchodilating) potency of TD-4208 on acethylcholine-induced contraction of tracheal rings, which was found to be similar to that obtained on human recombinant receptors. The sustained inhibitory effects of TD-4208 on electrical field-stimulated contractions of the tracheal ring preparations were found to last >16 h [9,10].

In vivo testing comparatively evaluated the pharmacological properties (bronchodilating potency, duration of action, and M3 selectivity) of TD-4208, glycopyrronium, and tiotropium in rats and dogs separately for single or repeated (seven) doses. Bronchodilating potency and onset of action at various single doses (3, 10, and 30 mg/kg) of inhaled TD-4208 were tested in dogs. A dose-dependent bronchodilating effect, which was significantly superior to that of placebo (inhaled vehicle), was observed. The onset of action for all doses was 5 min after dosing. The duration of bronchodilating effect was also found to be dose dependent, with only two higher doses resulting in >24 h sustained inhibitory effects. The other two LAMAs tested were also found to exert significant antimuscarinic effects compared with placebo [8,9]. Similar effects were found with both single and multiple doses on methacholine-induced bronchoconstriction in rats. The dose producing 50% inhibitory effect (ID50) was 45 mg/mL with single dosing and 36 mg/mL for repeated dosing.

In the latter category of animals, the selectivity of the three LAMAs was evaluated with the antisialagogue effect and lung selectivity index. Antisialagogic effects of TD-4208 were found to be dose dependent and had an estimated potency of 794 mg/mL with repeated dosing. Lung selectivity indexes were found to be comparable with both single and repeated dosing (26 versus 22) [8,9].

The inhibitory potential of revefenacin was also tested ex vivo in human airways in two sets of experiments: static tissue bath and perfusion washout studies. In the former set, concentrations of revefenacin ranging from 1 to 1000 nmol/L inhibited carbachol-induced contraction of the smooth muscle cells in a dose-dependent manner (9–70%). Concentrations of revefenacin 30 nmol/L, ipratropium 10 nmol/L, and tiotropium 10 nmol/L were considered equivalent in their miorelaxing effect. In the second set of experiments, the sustained inhibitory effect of revefenacin was demonstrated with the persistence of at least 50% inhibitory effect (t1/2, inhibition half-life) on carbachol-induced contraction of smooth muscle cells of >10 h after revefenacin 10 nmol/L was added to the human tissues. Tiotropium produced a comparable inhibitory effect at a concentration of 10 nmol/L, whereas a similar concentration of ipratropium was associated with a t1/2 of 2.9 h [9].

4. Pharmacodynamics

Pharmacodynamics of revefenacin were evaluated in two phase II studies after single dosing (STD1) and multiple ascending dosing for 7 days (STD2) [11]. The inclusion criteria in both studies were age of at least 40 years, airway obstruction (FEV1/FVC<0.7; FEV1%predicted 35–80% after bronchodilator

interruption, 6 h for short-acting bronchodilators and 24 h for long-acting bronchodilators), and ipratropium reversibility (increase after 400 µg ipratropium inhaled from a pressurized device of 12% and 200 mL in a single dose and 12% and 120 mL after nebulized ipratropium 500 µg in multiple doses).

Patients with SD1 were randomized to receive via nebulization, one of the four sequences comprising revefenacin 350 µg, 700 µg, placebo, or ipratropium 500 µg in a cross-over manner. Each dose was followed by a washout period of 7–12 days. Patients with SD2 were randomized to receive one of the 60 therapeutic sequences, including nebulized placebo and four of the following revefenacin doses (22, 44, 88, 175, 350, or 700 µg) for 7 days. Patients with SD1 were not allowed to use inhaled short-acting bronchodilators 12 h and tiotropium 72 h prior until 25 h after the dosing. In the STD2 study, short-acting bronchodilators were not allowed 12 h prior to the first dose until day 7, ipratropium bromide was not allowed 24 h prior to the first dose until day 8, and LAMAs and long-acting beta 2 agonists (LABAs) were not allowed 5 days prior to the first dose.

In the STD 1 study, the primary pharmacodynamic (PD) endpoint was represented by the change in peak FEV1 from baseline.

Secondary endpoints were represented by trough FEV1 and area under FEV1-time curve (AUC0–12 h) 12–24 h post-dose (AUC12–24 h). In the STD2 study, the PD endpoint was represented by the trough FEV1 after the seventh dose. Secondary endpoints were changed in peak FEV1 and AUC0–12 h, 12–24 h, and 0–24 h from baseline. Pharmacokinetics were evaluated in both studies. Intention-to-treat populations included 32 patients with STD1 and 62 patients with STD2.

In the STD1 study, both revefenacin and ipratropium doses significantly improved the PD endpoint compared to placebo (treatment difference versus placebo, 176.8 mL for revefenacin lower dose, 162.2 mL for revefenacin higher dose, and 190.6 for ipratropium, $p \leq 0.0001$) for all comparisons. Trough FEV1 was also found to be significantly improved by both revefenacin doses compared to placebo (treatment difference versus placebo, 102.8 mL for revefenacin lower dose, 136.6 mL for revefenacin higher dose, $p \leq 0.0001$). Revefenacin exhibited an onset of action similar to that of ipratropium bromide within the first 45 min after dosing, and the peak FEV1 value was recorded 2–3 h after dosing. The sustained bronchodilating effects of revefenacin were confirmed with similar values in the AUCs 12–24 h to 0–12 ratio (0.969 and 0.989, respectively).

In the STD2 study, the trough FEV1 at day 8 was significantly improved with all revefenacin doses compared to placebo ($p \leq 0.0006$). Furthermore, a dose-response effect was also found for this endpoint with doses from 22 to 175 µg with no further improvements with the higher doses (treatment differences versus placebo, 53.5 mL with 22 µg, 55 mL with 44 µg, 75.4 mL with 88 µg, 114.2 mL with 175 µg). The peak FEV1 after the first dose also significantly improved with all revefenacin doses, and the treatment difference ranged from 67.1 mL to 142.8 mL ($p < 0.001$ for all comparisons). The onset of action was detected within the first hour after dosing, and the effect was found to be persistent over the 7-day dosing period with ratios of areas under the curve of comparable value (0.969 to 0.979) [11].

5. Pharmacokinetics and metabolism

Pharmacokinetic (PK) analysis was performed in the two phase II PD and PK studies previously described, the two STD1 and STD2 studies described above, and further two phase II studies performed in patients with renal and hepatic impairment [11,12].

he pooled data analysis of STD1 and STD2 demonstrated that revefenacin was rapidly absorbed from the airways into the bloodstream and exhibited a biphasic elimination pattern consisting of a rapid reduction in plasma levels followed by slower terminal elimination. In both studies, the revefenacin Tmax was 0.33 h in STD1 and 0.233 in STD2 at a concentration of 350 µg and 0.317 h in STD1 and 0.250 in STD2 at a concentration of 700 µg. Cmax was 0.12 ng/mL at 350 µg and 0.25 ng/mL at 700 µg in STD1. In STD2, a dose-dependent increase in Cmax was demonstrated with values of 0.24 ng/mL at 350 µg and 0.53 ng/mL at 700 µg. Elimination half-time (t1/2) was 3.75 h at 350 µg and 6.65 h at 700 µg in STD1, whereas t1/2 at day 7 ranged from 22.3 to 25.3 h in STD2 [11,13]. Revenefacin was demonstrated to undergo quasitotal metabolism at the hepatic level through hydrolysis, resulting in THRX-195518, which is its major active metabolite considered to be responsible for systemic antimuscarinic effects. Revefenacin exhibited limited renal elimination. Consequently, renal elimination of the active compound was limited, with urinary cumulative amounts of <0.2%. In STD2, the plasma accumulation of the active compound of its metabolite was both dose dependent, but a limited and steady state was reached at day 7 [11,13].

PKs of single-dose inhaled revefenacin and its metabolite THRX-195518 were also evaluated in subjects with renal and hepatic impairment in two individual open-label studies [12]. These two open-label, parallel-group, single-dose phase II studies enrolled patients with severe renal and moderate hepatic failures and healthy controls. Each study enrolled 16 subjects: 8 subjects with organ impairment sample and 8 normal controls. In the renal impairment study, both plasma revefenacin and THRX-195518 levels were higher in patients with organ impairment than in normal controls (Cmax 0.267 at 0.196 ng/mL versus 0.068 at 0.040 ng/mL). The same trend was found with elimination half-life t1/2 of 35.3 in 29.7 h for the active substance and 6.69 h for the metabolite in the renal impairment study [12].

In the hepatic impairment study, a similar pharmacological profile was characterized by an initial rapid absorption phase to Cmax, followed by a rapidly declining concentration and slower elimination half-life, which were comparable between the groups (Cmax 0.23 ng/mL in subjects with hepatic impairment versus 0.22 ngmL in normal subjects; t1/2, 29.8 and 30.3 h, respectively) [12].

The PK analysis in the 28-day phase II dose-ranging study described in detail below showed a Tmax ranging from 0.48 h to 0.517 h, Cmax from 0.02 to 0.146 ng/mL, and an elimination half-life of 51.9 h at 175 µg and 57.9 h at 350 µg. The mean AUC of plasma revefenacin levels for 24 h ranged from 0.034 to 0.36 ng/mL [14].

Table 1. Clinical studies evaluating revefenacin in COPD patients.

Authors	Clinical phase/ comparator	ITT population	Duration and dosages	Primary endpoint/ improvement	Secondary endpoints
Pudi et al. [13]	II/placebo	354	28 days 44, 88, 175, or 350 µg	Trough FEV1 at day 29 Yes	Change in pre-dose FEV1 at 6 hours (day 1) 12,24(day 28) Time to increase in FEV1 by 100 ml Change in baseline post-bronchodilator FEV1 Change in baseline PEF Rescue medication use
Donohue et al. [17]	III/tiotropium	1055	52 weeks Revefenacin 88, 175 µg Tiotropium 18 µg	Trough FEV1 at the end of treatment period Yes	Change from baseline in health status(CAT, CCQ, SGRQ questionnaires) Change from baseline in dyspnea (BDI/TDI indexes) Exacerbation severity (EXACT-PRO) Rescue medication use
Ferguson et al. [18]	III/placebo	1230	12 weeks Revefenacin 88, 175 µg Placebo	Trough FEV1 on day 85 Yes	Change from baseline in health status(SGRQ questionnaires) Change from baseline in dyspnea (BDI/TDI indexes) Rescue medication use
Mahler et al. [19]	III/tiotropium	206	28 days Revefenacin 175 µg Tiotropium 18 µg	Trough FEV1 at day 29 Yes	Trough FVC and IC peak FEV1 and FVC PEF increase rescue medication use

6. Clinical efficacy

Clinical efficacy was evaluated in phase II and III studies usually enrolling patients with moderate to very severe COPD and analyzing the usual endpoint measures used in clinical development for inhaled drugs (trough FEV1, use or rescue medications, etc.). Table 1 presents the existing efficacy data.

6.1. Phase I studies

A phase I study was performed in healthy individuals to investigate the safety and tolerability of two single doses of inhaled revefenacin (one being further tested in other stages of clinical development in patients with COPD and the higher one being considered supratherapeutic and only used for safety analysis purposes). The results of this study are described in more detail in the safety section [15].

6.2. Phase II studies

The four phase II studies were performed to assess PD, PK, safety, and tolerability in various meaningful populations, including patients with COPD, and their results are discussed in the specific sections [11,12].

Another phase II study evaluated the efficacy, PK, safety, and tolerability of various doses of revefenacin in a 28-day period [16]. This was a randomized placebo-controlled dose-ranging study in which the primary endpoint was represented by the change in baseline in trough FEV1 at the end of the dosing period (on day 29). The secondary efficacy endpoints included change from pre-dose level in mean FEV1 measured during day 1 after 6 h from dosing, change from a pre-dose level in mean FEV1 after 12 and 24 h at day 28, time to a 100 mL increase of baseline post-bronchodilator FEV1, change in baseline PEF, and rescue medication use. PK analysis included calculation of Tmax, Cmax, elimination half-life, and AUC for plasma levels in 24 h and at last detectability moment. Safety analysis included reporting of treatment-related adverse events [14].

The intention-to-treat population included 354 patients with COPD, mostly current smokers (53.7%). Moreover, 43.6% of patients received either nebulized placebo or revefenacin 44, 88, 175, or 350 µg once daily. The primary endpoint improved significantly with the three highest revefenacin doses compared with placebo (187.4 mL with 88 µg, 166.6 mL with 175 µg, and 170.6 mL with 350 µg, $p < 0.001$ for all comparisons). All four doses showed significant improvement in mean baseline FEV1 6 h from dosing compared with placebo (111.7 mL, 160.5 ml, 146.7 mL, and 181.5 mL each for the corresponding dose tested, $p < 0.001$). The three highest doses were also associated with significant reductions in the rescue inhaler compared to placebo and produced an increase in PEF, which became significant after the sixth dose and was maintained in a 28-day dosing period [14].

6.3. Phase III studies

Phase III studies were done to assess the long-term efficacy and safety of nebulized revefenacin in patients with COPD and performed similar analyses over variable periods in subsets of patients with COPD considered to be potential best beneficiaries of the investigational therapy. These subsets were represented by patients with functionally advanced disease (severe to very severe COPD) and those with impaired inspiratory flow.

A phase III study evaluated the efficacy, safety, and tolerability of revefenacin doses of 175 µg and 88 µg and tiotropium 18 µg in 52 weeks, which included 1055 patients with COPD. Exploratory efficacy endpoints included trough FEV1 at the end of the treatment period, change in health status from baseline measured using three different disease-specific questionnaires (St. George's Respiratory Questionnaire [SGRQ], CAT, and CCQ), dyspnea dynamics from baseline, severity of exacerbations with EXACT-PRO, and need for rescue medication [17,18]. Both LAMAs significantly increased the baseline trough FEV1 at the end of treatment period

(48.8 with revefenacin 88 µg, 52.3 with revefenacin 175 µg, and 91.5 with tiotropium, $p < 0.003$ for all comparisons). Subgroup analysis performed in patients with COPD using LABA demonstrated that significant improvement was induced by both LAMAs. Health status improved at the end of 52 weeks, and proportions of patients exhibited clinically significant improvements in health status as measured with SGRQ (53%, 42%, and 45%). Clinically significant improvements in dyspnea were reported in 43.8% of patients administered with revefenacin 175 µg, 50.9% of patients administered with revefenacin 88 µg, and 40.3% of patients administered with tiotropium 18 µg. The number of rescue bronchodilator use was 1.6/day with revefenacin 175 µg, 1.9/day with revefenacin 88 µg, and 1.3/day with tiotropium. The exacerbation rate was 1.78 with revefenacin 175 µg, 2.46 with revefenacin 88 µg, and 2.31 with tiotropium [18].

Two paired phase III randomized placebo-controlled studies evaluating the safety, efficacy, and tolerability of two doses of revefenacin (88 or 175 µg) administered once daily in 12 weeks in patients with moderate to very severe COPD. Patients with disease severity ranging from moderate to very severe were included. The primary efficacy endpoint was represented by the change in trough FEV1 from baseline on day 85. Secondary efficacy endpoints were represented by the overall treatment effect (OTE) on trough FEV1, health status change measured with the SGRQ, rescue albuterol salbutamol use, and dyspnea severity. Safety endpoints were also included.

A total of 619 patients was enrolled in the first study (STD1): 212 receiving 88 µg, 198 receiving 175 µg, and 209 receiving placebo. Moreover, 611 were included in the second study (STD2): 205 receiving 88 µg, 197 receiving 175 µg, and 209 receiving placebo.

The mean age ranged from 63.1 to 64.3 years, in two arms (one placebo in STD2 and one 175 µg in STD 1). Most patients were female, and in the remaining arms, male sex was prevalent. The proportion of current smokers varied from 45.7% to 49.3%. The mean post-ipratropium FEV1% predicted ranged from 53.5% to 55.9%. Most enrolled patients had no exacerbations over the previous year, and the baseline health status was measured with CAT of at least 10. Compared to placebo, revefenacin significantly improved the primary efficacy endpoint at both dosages (mean increase in trough FEV1, STD1 79.2 mL with 88 µg, $p = 0.0003$, and 146.3 mL, 175 µg, $p < 0.0001$; STD2 160.5 mL with 88 µg, $p < 0.0001$, and 147 mL, 175 µg, $p < 0.0001$; pooled effect 119.8 with 88 µg, $p = 0.0003$, 148.1 mL, 175 µg, $p < 0.0001$). OTE increased significantly with revefenacin in both studies (≥100 mL; pooled data 115.3 mL with 88 µg and 142.3 mL with 175 µg). Trough FEV1 was found to significantly increase within the next 2 h from the first revefenacin dosing in both studies. Placebo-adjusted peak FEV1 (achieved in the first 2 h after dosing) increased by 127.3 mL with revefenacin lower dose and 129.5 mL with revefenacin higher dose. Pooled data analysis demonstrated a dose-dependent improvement in the primary efficacy endpoint, the higher dose arm included more patients with severe COPD receiving concomitantly LABA/inhaled corticosteroid combinations [19].

A phase IIIb randomized placebo-controlled study was performed in 206 patients with COPD and a suboptimal inspiratory peak flow rate (PIFR), which has a threshold defining the value of <60 L/min while breathing through a dry powder inhalation device (Diskus) [20]. Eligible patients with COPD received nebulized revefenacin (175 µg) once daily or dry powder tiotropium (18 µg) with appropriate blinding of the therapies maintained throughout the study. The primary endpoint was similar to that of the other phase II or III studies and represented by the change in trough FEV1 from baseline. In this study, this was measured at day 29 and rescue albuterol use in the study period. Secondary endpoints included trough FVC, inspiratory capacity and peak FEV1, and FVC (in the first 4 h after dosing), all measured at the same time point. In a post hoc analysis, the primary endpoint was analyzed in five comparable subsets of patients defined by PIFR quintile values (<33 L/min, 33–45 L/min, 45–52 L/min, 52–56 L/min, and 56–60 L/min). Efficacy analysis was performed in 206 patients, and the sample included 49.6% of elderly patients with a mean FEV1 of 36.8% and mean PIFR of 45 L/min and a small proportion of previous year exacerbators (9.2% overall). This makes this sample relevant to the analysis because elderly patients with milder COPD can also have an age-related reduction in PIFR.

Revefenacin was superior to tiotropium in improving trough FEV1 in the whole sample and patients (57.9 versus 40.9 mL; 72.3 versus 23.2 mL). Revefenacin was associated with numerically higher increases in trough FVC and IC than tiotropium in most of the subset analyses (revefenacin versus tiotropium, trough FVC, 118.4 versus 46.9 mL; in patients with severe to very severe COPD, 141.4 mL versus 37.9 mL; trough IC, 71.8 mL versus 82.9 mL; in patients with severe to very severe COPD, 83.6 mL versus 67.4 mL) [20,21]. Trough FEV1 analysis by PIFR quintiles subsets in the whole sample and FEV1 < 50% subsample demonstrated that revefenacin exhibited superior effect in 33–45 L/min quintile in both analyses and 45–52 L/min and 52–56 L/min in severe COPD analysis. Revefenacin and tiotropium produced comparable increases in peak FVC or PEF and trough IC at day 29 [20]. The rescue albuterol use did not differ between the two LAMAs (3.4/day versus 2.9/day).

7. Safety and tolerability

The safety and tolerability of nebulized revefenacin were evaluated in a phase I study performed in healthy subjects and phase II and III studies involving patients with COPD or those with other conditions.

In the phase I study, the primary endpoint was the placebo-adjusted change in QTc from baseline after each of the two administered doses (175 µg, therapeutic dose, and 700 µg, supratherapeutic dose), and this was found to be close to 0 for both doses. No clinically significant increases in heart rate were reported. Both doses were well tolerated [15].

In phase II PD and PK studies, it was reported that revefenacin was well tolerated and the adverse events were mostly mild and with similar incidences among treatment groups [12]. No adverse events related to muscarinic receptor blockade (dry mouth, urine retention, acute closed-angle glaucoma, or tachycardia) were reported in both studies. In the STD1 study, headache and dyspnea were the most commonly reported adverse events

with single dosing (28.1%, 18.8%), and no serious adverse events were reported. In the STD2 study, the safety profile was found to be similar, with dyspnea, headache, and cough. Serious adverse events were reported in three patients, whereas study drug discontinuation was necessary in five patients. No ECG abnormalities were reported in these studies [11].

Safety and tolerability were also evaluated in two open-label studies enrolling patients with renal and hepatic impairment [12]. Treatment-related adverse events were found to be mild to moderate in both studies, and no severe or serious events, including death, were reported. No study drug discontinuation was necessary. In the renal impairment study, treatment-related adverse events had similar incidences in subjects with impairment and normal subjects (25%). These were represented by dizziness and headache in normal subjects and upper respiratory tract infection, dizziness, and throat irritation in subjects with renal impairment. In the hepatic impairment study, the incidence of such events was 12.5% in normal subjects and 25% in patients with hepatic impairment: mild chest discomfort in the former group and diarrhea and dizziness in the latter group [12]. No significant QTc prolongation was reported in both studies.

In the dose ranging phase II study, discontinuation due to an adverse event was reported in 3.4% of the patients who more often belonged to the two highest doses of revefenacin. All adverse events were self-resolving except for an episode of respiratory distress reported in a patient in the placebo group. The adverse events most commonly reported were headache, shortness of breath, and cough, with overall incidences of 3.1%, 2.85%, and 2%, respectively. Four COPD exacerbations were also reported. Four serious adverse events were reported, three of which were cardiovascular (1 episode of supraventricular tachycardia in 44 µg dose, one episode of unstable angina, one episode of hypertension in the 175 µg arm, and one intestinal occlusion in the highest revefenacin dose arm). Antimuscarinic effects were only represented by dry mouth, which was only reported twice [14].

In the 52-week phase III study, general and cardiovascular safety analyses were performed [18,22–24]. In the general safety analysis, the incidences of serious adverse events (15.9% with revefenacin lower dose, 12.8% with revefenacin higher dose, and 16.3% with tiotropium) and treatment-related adverse events (74.7% with revefenacin lower dose, 72.2% with revefenacin higher dose, and 77.2% with tiotropium) were comparable between revefenacin and tiotropium groups. No dose-related increases in the incidences of these two categories of adverse events were found in revefenacin population. The proportion of patients with at least one adverse event was 74.8%. COPD was the most commonly reported treatment-related adverse event across study arms (29.4% with revefenacin lower dose, 21.8% with revefenacin higher dose, and 77.2% with tiotropium 28.1%). Cardiovascular safety analysis reported comparable incidences (QTc interval prolongation, 4.4% with revefenacin lower dose, 7.7% with revefenacin higher dose, and 7.3% with tiotropium) [22]. A total of 26 major adverse cardiovascular events were reported: 9 with revefenacin lower dose, 10 with revefenacin higher dose, and 7 with tiotropium.

In the paired phase III studies, the overall incidence of treatment-related adverse events was similar among the two treatment arms and placebo. The proportion of patients with at least one adverse event varied across the treatment arms, from 47% to 57% of the patients. The most common adverse event was COPD exacerbation, which was reported in 12.2% of patients, followed by headache (6.8%), respiratory infection (6.6%), dyspnea (5.7%), and cough (5.1%) with no significant differences across the treatment groups. The incidences of muscarinic-blockade-related side effects were comparable in both treatment and placebo groups. The most common were constipation (six patients) and dry mouth (four patients). The incidences of serious adverse events were similar for both active treatment and placebo (6.7% and 5.4% in each of the two studies) [19]. Incidences of QTc interval prolongation in pooled safety population were 5.6% with revefenacin lower dose, 5.9% with revefenacin higher dose, and 5.3% with placebo [22].

In a phase IIIb study performed in patients with suboptimal PIFR, fewer adverse events were reported with revefenacin than those with tiotropium. The most common treatment-related adverse events were dyspnea and cough with both LAMAs.

Patients receiving tiotropium reported more treatment-related adverse events than patients receiving revefenacin [20].

8. Regulatory affairs

Revefenacin for nebulization use is currently approved for COPD maintenance therapy only in the USA and currently evaluated for the same indication by other regulatory bodies worldwide.

9. Expert opinion

In COPD, inhaled LAMAs play a prominent role in maintenance therapy in the stable state of the disease because chronic airway inflammation is mainly associated with an upregulated muscarinic pathway, resulting in sustained airway obstruction and progressive dyspnea and cough. The first LAMA approved for use in COPD was tiotropium bromide (Spiriva®), which has been considered for many years since its authorization as the first-line therapy (and monotherapy) in patients with stable COPD. However, this compound was initially formulated to be used as dry powder inhalation therapy (capsules delivered once daily through a HandiHaler). This type of inhaled device was found to have limited effectiveness in patients with more advanced disease, and hence it was reformulated as a soft mist inhalation therapy delivered via an inhalation device, which can be considered as a hybrid between a metered dose inhaler and nebulizer. The next three LAMAs approved for similar indication were glycopyrrolate, aclidinium, and umeclidinium, which were all formulated for dry powder inhalation use and are not available worldwide as monotherapies for stable COPD. Among these, aclidinium bromide is more commonly used in combination with formoterol and dosed twice a day in patients with residual or rebound respiratory symptoms at night or early morning [25,26]. These LAMAs are formulated as dry powder inhalers and have a lower likelihood of reaching the smaller-caliber airways in patients with impaired inspiratory effort, specifically patients with severe and very severe functional stages of COPD. In such patients, metered dose inhalers are

demonstrated to be more efficient, but the dosing through such devices requires a excellent coordination of breathing stages (inspiration/expiration), which cannot be achieved on a sustained basis exactly by such persons, especially if they are aged or with cognitive impairments. An even better option would be represented by nebulization, which does not involve any coordination with breathing and is not dependent on the amplitude of the inspiratory force but requires longer administration times. However, in COPD, nebulized formulations are short-acting bronchodilators needed to be dosed 3–4 times a day and used more commonly in acute exacerbations.

Revefenacin is a LAMA with a rapid onset of action (reported to be approximately 5 min from dosing), formulated for nebulization, and dosed once daily. If it can be used with any type of nebulizer and if its price is not extremely high, such medication can become an important player in the LAMA market. However, if long-term efficacy appears to be sustained, especially in patients with severe to very severe COPD, the long-term safety and its effects on lung function decline, and exacerbation rate are still to be documented by post-marketing studies.

Given its fast onset of action and the fact that it can be administered via the nebulization route, revefenacin might also be evaluated in the setting of COPD exacerbations as standalone or in combination with a nebulized LABA with comparable onset of action such as formoterol.

Even if it is a newcomer on the inhaler market, revefenacin holds promise because of the particular pharmacologic profile and well-awaited method of administration, which is unique for this once daily formulation.

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