

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210598Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sally Seymour, MD
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA 210598
Applicant	Theravance
Date of Submission	November 13, 2017
PDUFA Goal Date	November 13, 2018
Proprietary Name	Yupelri
Established or Proper Name	Revefenacin
Dosage Form(s)	Inhalation solution
Applicant Proposed Indication(s)/Population(s)	(b) (4) maintenance treatment of (b) (4) in patients with chronic obstructive pulmonary disease (COPD)
Action or Recommended Action:	<i>Approval</i>
Approved/Recommended Indication(s)/Population(s) (if applicable)	Maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Khalid Puthawala
Statistical Review	Dong-Hyun Ahn
Pharmacology Toxicology Review	Eleni Salicru/Tim Robison
OPQ Review	
Microbiology Review	
Clinical Pharmacology Review	Renu Singh
OPDP	Taylor Burnett
OSI	Lakisha Williams/Yolanda Patague Min Lu
CDTL Review	Robert Lim
OSE/DEPI	
OSE/DMEPA	Lissa Owens
OSE/DRISK	Robert Pratt
OSIS/DNDBE	Zhou Chen, Yiyue Zhang, Charles Bonapace
DMPP	Nyedra Booker

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

COPD is a debilitating respiratory condition that involves significant morbidity and mortality; it is the third leading cause of death in the US. A large amount of healthcare resources is utilized in managing long-term COPD as well as treating acute exacerbations. It is often associated with active or prior cigarette smoking (typically > 10 pack-years), but other environmental and genetic factors have been found to contribute to its etiology. Multiple treatment options exist, but no once-daily nebulized anticholinergic medication is approved.

The Applicant has submitted an NDA for revefenacin (tradenname Yupelri), a new molecular entity anticholinergic, for the proposed indication of (b) (4) maintenance treatment of (b) (4) COPD at a proposed dose of 175 mcg delivered via a general use jet nebulizer once daily. To support this application, two 12-week placebo-controlled studies were conducted, as well as a 52-week active-controlled safety study.

In the 12-week bronchodilator studies, revefenacin demonstrated statistically significant improvements versus placebo in change from baseline in trough FEV1 at day 85. Efficacy was further supported by secondary spirometric endpoints (trough FEV1 over the treatment period and peak FEV1). Additionally, the proportion of patients who experienced improvements in symptoms as measured by SGRQ (a patient reported outcome questionnaire for COPD) was numerically higher than placebo in both studies. A 52-week active controlled safety study was also performed, and findings were consistent with safety data from the 12-week studies and did not reveal any new safety issues that would offset the efficacy benefits. Efficacy and safety results across various demographic and baseline disease characteristic subgroups were consistent with the overall findings.

This risk-benefit assessment of revefenacin is favorable. Submitted data from adequate and well-controlled trials demonstrates the efficacy of revefenacin as a bronchodilator. The safety issues identified can be managed by labeling. Approval of this product provides a new inhalation solution option for a long-acting anticholinergic for patients with COPD.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • COPD is a debilitating respiratory condition that involves significant morbidity, mortality, and healthcare resource utilization. • COPD primarily affects tobacco users over 40 years of age; it is the third leading cause of death in the US and rates continue to rise. • Common symptoms of COPD include one or more of the following: dyspnea, fatigue, cough, sputum production, chest tightness, wheezing, worsened exercise capacity, depression, anxiety, weight changes. • Diagnosis primarily rests on spirometry; a decreased FEV1/FVC ratio < 0.7 is used for diagnosis of COPD in the GOLD guidelines. • Treatment primarily involves use of inhaled medications for symptom control of acute exacerbations and chronic long-term maintenance; other treatment adjuncts (e.g. tobacco cessation, pulmonary rehabilitation, oxygen use) are important as well. 	<p>COPD is a common debilitating respiratory condition causing significant morbidity and mortality. The diagnostic and symptom assessment instruments used by the Applicant are reasonable to assess COPD.</p>
Current Treatment Options	<ul style="list-style-type: none"> • Several classes of inhaled medications exist for the maintenance treatment of COPD: Anticholinergics, long-acting beta₂-agonists, and combination products (with and without ICS). • There are currently no long-acting, once daily nebulized long acting anticholinergics for COPD. 	<p>Multiple inhaled medications are available for COPD within a variety of drug classes; however, no long-acting, once daily, nebulized anticholinergic is currently available.</p>
Benefit	<ul style="list-style-type: none"> • The Applicant has demonstrated substantial evidence of efficacy for revefenacin in moderate-to-very severe COPD patients based on statistically significant improvements in trough FEV1 at day 85, with support from other spirometric endpoints (trough FEV1 over the treatment period and peak FEV1), as well as numerical improvements in symptoms based on St. George's Respiratory Questionnaire (SGRQ) responder analysis. 	<ul style="list-style-type: none"> • Revefenacin provides clinically relevant treatment benefits as a bronchodilator in moderate-to-very severe COPD patients. • Revefenacin provides a new inhalation solution option for a long-acting anticholinergic for patients with COPD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none"> The safety program for revefenacin demonstrated no new concerning safety signals beyond that seen with medications in its class. 	<ul style="list-style-type: none"> No safety findings were identified in the clinical development program that outweigh the potential benefit. Labeling and routine pharmacovigilance alone are recommended.

1. Background

Theravance submitted a 505(b)(1) New Drug Application (NDA) 210598 on November 13, 2017, for revefenacin inhalation solution (REV) for the proposed indication of (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). The proposed tradename is Yupelri. REV is a long-acting anticholinergic and is formulated as a solution for inhalation in a unit-dose vial to be delivered via a general use nebulizer. Revefenacin would be the first, once daily, long-acting anticholinergic to be administered by nebulization with a standard jet nebulizer. As described in this memo, Theravance conducted a clinical program that includes multiple dose-ranging trials, two confirmatory phase 3 clinical trials, and one long-term safety trial.

There are several drug classes available for the treatment of airflow obstruction in patients with COPD. These include long-acting beta-2 adrenergic agonists, long-acting anticholinergics; combination products containing long-acting beta-2 adrenergic agonists (LABA) and long-acting anticholinergics (antimuscarinics) [LAMA]; combination products containing LABA and corticosteroids; combination products containing LABA, corticosteroids, and LAMA; products containing methylxanthines; and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include LABA, combination products containing LABA and inhaled corticosteroids (ICS), LAMA, and PDE-4 inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

REV is a long-acting anticholinergic and is new molecular entity (NME). It is not marketed in any country as a monotherapy or in fixed-dose combination with other therapies.

Inhaled anticholinergics are widely available in the U.S., including one short-acting anticholinergic, ipratropium bromide, and four LAMA, tiotropium bromide (Spiriva HandiHaler, Spiriva Respimat), aclidinium bromide (Tudorza Pressair), glycopyrrolate (Lonhala Magnair, Seebri Neohaler, and in combination with indacaterol as Utibron Neohaler), and umeclidinium (in combination with vilanterol as Anoro Ellipta, with vilanterol and fluticasone as Trelegy Ellipta, and as single ingredient Incruse Ellipta). All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention.

In the past, safety concerns of stroke and cardiovascular death have been raised with the use of these drug products in patients with COPD, and thus have been the subject of previous FDA advisory committee meetings.¹ These concerns have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat.^{2, 3} Nevertheless, it is important to

¹ FDA Early Communication about Ongoing Safety Review of Tiotropium. http://www.fda.gov/cder/drug/early_comm/tiotropium.htm

² Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Eng J Med* 2008; 359: 1543-54.

³ Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Eng J Med* 2013; 369:1491-501.

select an appropriate dose and dose regimen for any anticholinergic in a COPD program to limit high systemic exposure and potential safety concerns.

2. Product Quality

The recommended action from a CMC/Quality perspective is Approval.

Drug Product and Drug Substance

Revefenacin is an anticholinergic compound that acts as a muscarinic receptor antagonist. Revefenacin, free base, is an anhydrous, crystalline, and thermodynamically stable form that is highly soluble in aqueous buffered solution at pH 5. The drug product is formulated with compendial grade excipients, (b) (4) will be marketed (175 mcg). The drug product formulation is an isotonic, sterile aqueous solution containing sodium chloride, citric acid, and sodium citrate, at pH 5.0. The solution is packaged in a low density polyethylene, or LDPE, container with a foil laminate overwrap. Theravance provided adequate extractables and leachables data and stability data to support a 24-month shelf-life. The sterility testing procedure is acceptable, as are the proposed storage condition and shelf-life for the drug product, from a microbiology perspective.

The drug substance is proposed for manufacturing in a site in (b) (4). The site is recommended as adequate for the operations outlined in NDA 210598. The drug product, revefenacin inhalation solution, is proposed for manufacturing at a site in (b) (4). The site is also recommended as adequate for the operations outlined in NDA 210598.

Revefenacin is proposed to be delivered via a 510K-cleared general use nebulizer.

3. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical pharmacology/toxicology issues.

The Applicant has performed a complete nonclinical program for REV. There are no outstanding nonclinical issues. Pharmacology studies demonstrated that revefenacin is a muscarinic receptor antagonist with similar affinity for all five human muscarinic receptor subtypes (hM1 to hM5). In the airways, the pharmacological action of revefenacin was mediated primarily through inhibition of the M3 receptor at the smooth muscle, leading to bronchodilation. Based upon available data, it was determined that there is an active metabolite, THRX-195518.

Nonclinical toxicology studies provide adequate safety margins for clinical exposures to revefenacin and THRX-195518. Chronic inhalation toxicology studies with revefenacin were conducted in rats (26 weeks) and dogs (39 weeks). Pharmacodynamic effects were observed

in dogs, including increased heart rate, which is considered adverse, but monitorable in the clinical setting. The most notable histopathology findings in rats were identified in the larynx (hyperplasia/metaplasia, exudate, and mononuclear cell inflammation of epiglottis) and judged to be nonspecific irritant effects associated with the aerosol inhalation and not considered relevant to humans. There were no notable histopathology findings in dogs.

Revefenacin was negative for the standard battery of in vitro and in vivo genotoxicity assays. Its metabolite, THRX-195518, was negative in an in vitro Ames bacterial reverse mutation assay. There was no evidence of tumorigenic potential for revefenacin in 2-year carcinogenicity studies conducted in CD-1 mice and Sprague-Dawley rats.

Theravance conducted reproductive toxicity studies with revefenacin that included a fertility and early embryonic development study in rats, embryo-fetal development studies in rats and rabbits, and a pre- and post-natal development study in rats. Revefenacin did not affect fertility or reproductive performance in male and female rats treated with doses of revefenacin up to 500 mcg/kg/day. In embryo-fetal development studies with pregnant rats and rabbits dosed during the period of organogenesis, revefenacin was not teratogenic and did not affect fetal survival at maternal subcutaneous doses up to 500 mcg/kg/day. Placental transfer of revefenacin and metabolite THRX-195518 was observed in pregnant rabbits. In a pre- and postnatal development study in pregnant rats dosed from gestation day (GD) 6 to lactation day (LD) 20, revefenacin had no adverse developmental effects on pups at maternal doses up to 500 mcg/kg/day. Revefenacin and metabolite THRX-195518 were present in milk of lactating rats on LD 22.

4. Clinical Pharmacology

The recommended regulatory action from a Clinical Pharmacology/Biopharmaceutics perspective is Approval. There are no outstanding clinical pharmacology issues.

The clinical pharmacology (CP) program for revefenacin solution for inhalation included the expected battery of studies, including a thorough QT study. There are two issues that are notable about the clinical pharmacology program.

One of the issues was the limited data in patients with hepatic impairment. Data showed that there is extensive hepatobiliary elimination of revefenacin and THRX-195518. While the Applicant conducted a hepatic impairment study, it was performed in patients with moderate hepatic impairment. This study showed an increase in the active metabolite exposure. Given the increased exposure to the active metabolite (THRX-195518) and the lack of data in patients with mild hepatic impairment, the product labeling states that revefenacin should not be used in patients with any degree of hepatic impairment.

Second, CP data from the phase 3 studies were determined to not be reliable. Review of the phase 3 CP data revealed that a significant percent (~22%) of pre-dose PK samples had detectable levels of revefenacin before Day 1 dosing. Seventy-five percent (75%) of the pre-dose positive samples had measurable revefenacin concentrations of 1- to 10-fold of the lower limit of quantitation (LLOQ), while the remaining 25% had concentrations >10-fold the

LLOQ. These findings suggested that sample switching had occurred in the phase 3 studies. The Applicant noted there could have been sample switching, insufficient ventilation, cleanability, timing of cleaning of surfaces, and contamination from personnel [same personnel were doing study visit procedures (i.e. nebulization) and lab draws potentially leading to pre-treatment positives if trace amounts of drug are retained on the clothing and transferred to tubes]. On inspection of the clinical sites, one site in phase 3 study 127 had not documented the date/time when PK samples were stored in the freezer or removed for processing. Due to these issues, the phase 3 PK data were deemed unreliable and were not used in CP analyses; however, the phase 3 PK data were not necessary for approval of revefenacin.

The major findings from the CP program are described in detail in Dr. Singh's clinical pharmacology review and summarized in Dr. Lim's CDTL review. Some of the key findings are outlined below:

- 1) Following administration of revefenacin inhalation solution by nebulization in healthy subjects or COPD patients, C_{max} of revefenacin and THRX-195518 occurred between 14 to 41 minutes after start of nebulization. The absolute bioavailability following administration of an oral dose of revefenacin is relatively low (<3%). Steady state was achieved within 7 days with <1.6-fold accumulation. Revefenacin systemic exposure increased in a slightly greater than dose proportional manner. The terminal plasma elimination half-life of revefenacin and active metabolite (THRX-195518) following once-daily dosing in COPD patients is 22 to 70 hours.
- 2) There is minimal renal excretion (<1%) of revefenacin and THRX-195518 following inhaled administration of revefenacin. These results indicate extensive hepatobiliary elimination of revefenacin and THRX-195518.
- 3) Following inhaled administration, the mean revefenacin C_{max} and AUC_6 values were approximately 66% and 56% lower, respectively, in COPD patients (Study 0091) as compared to healthy subjects (Studies 0134, 0135, 0136).
- 4) In severe renal impairment compared to normal renal function, there was a 1.5-fold increase in C_{max} of revefenacin and a 1.2 to 2-fold increase in C_{max} of THRX-195518. There was a 1.2 to 2.3-fold increase in AUC of revefenacin; THRX-195518 exposure (AUC) was increased by 1.6 to 2.5-fold. Based on these findings, the CP team has recommended that while no dose change is necessary in renal impairment, patients with renal impairment should be monitored for anticholinergic effects while on revefenacin.
- 5) In moderate hepatic impairment compared to normal hepatic impairment, there was no increase in C_{max} of revefenacin and a 1.5-fold increase in C_{max} of THRX-195518. There was a 1.2-fold increase in AUC of revefenacin; the THRX-195518 exposure (AUC) was increased by 2.8 to 4.7-fold. Given this increased exposure to the active metabolite (THRX-195518) and the lack of data in patients with mild hepatic impairment, the CP team recommends that revefenacin should not be used in patients with any degree of hepatic impairment.

5. Clinical Microbiology

The recommended regulatory action from a Clinical Microbiology perspective is Approval. There are no outstanding clinical microbiology issues.

The microbiology reviewer reports that the Applicant provided an adequate description of the drug product composition and the container closure system and how product sterility would be maintained. Container-closure integrity testing is performed on 100% of manufactured vials during commercial production and any leaking vials are rejected. This is consistent with regulatory expectations for a sterile pharmaceutical product. The microbial attributes of the drug product and drug product manufacturing were assessed and found to be acceptable.

6. Clinical/Statistical-Efficacy

Overview of the clinical program

The studies relevant to regulatory decision-making for this application are listed in Table 1.

Table 1. Relevant clinical studies with revefenacin inhalation solution in COPD patients

Study #	Study Design/ Population/	Regimen	Study Endpoints	Treatment Duration	Patients enrolled	# of Centers
Dose Ranging Studies						
91	R, DB, PC, CO Moderate to severe COPD patients	REV 22, 44, 88, 175, 350, and 700mcg INH daily Placebo	Trough FEV1	7 days	62	1 site in New Zealand 2 sites in United Kingdom
116	R, DB, PC, CO Moderate to severe COPD patients	REV 44mcg INH BID REV 175mcg INH daily Placebo	FEV1 AUC _(0-24 hrs)	7 days	64	4 sites in U.S.
117	R, DB, PC, Moderate to severe COPD patients	REV 44, 88, 175, and 350mcg INH daily Placebo	Trough FEV1	28 days	354	41 sites in the U.S.
Controlled Studies to Support Efficacy and Safety						
126, 127	R, DB, PC, PG Moderate to very severe COPD patients	REV 88mcg INH daily REV 175mcg INH daily Placebo INH daily	Trough FEV1 day 85 FEV1 overall treatment effect Rescue medication use Peak FEV1 SGRQ	12 weeks	126: 619 127: 611	0126: 60 sites (All US) 0127: 59* sites (All US)
Studies to Support Safety						
128	R, DB, AC/OL, PG Moderate to very severe COPD patients	REV 88mcg INH daily REV 175mcg INH daily Tiotropium 18 mcg INH daily	Safety	52 weeks	1080	103 sites (All US)

Abbreviations: INH- inhalation, R- randomized, DB- double-blinded, PC- placebo-controlled, PG- parallel group, AC/OL-

active comparator open-label, CO-cross-over

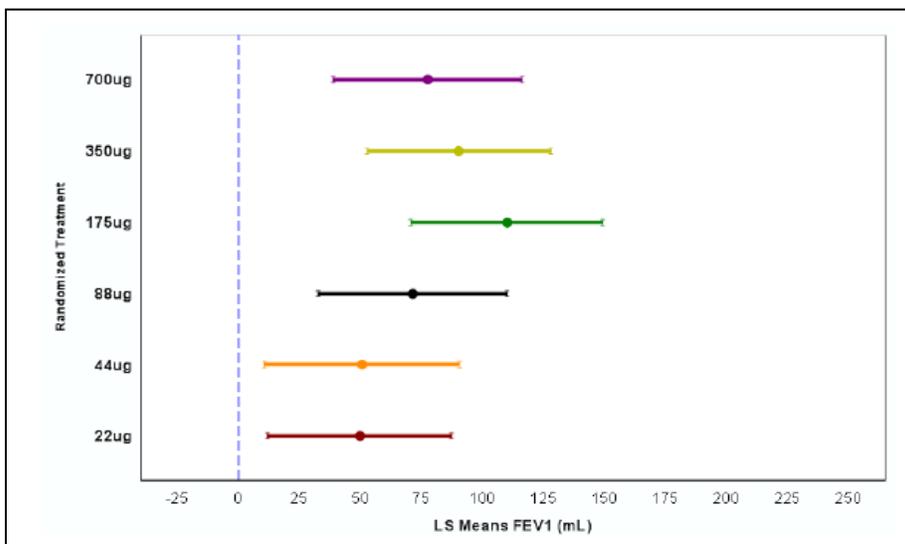
* Two sites excluded from efficacy analysis due to site misconduct found on sponsor's internal audit

Dose Ranging Studies: Studies 91, 116, and 117

The dose ranging studies were designed to characterize the dose-response for revefenacin. The study designs, treatment arms, and primary efficacy variable measured are shown in Table 1.

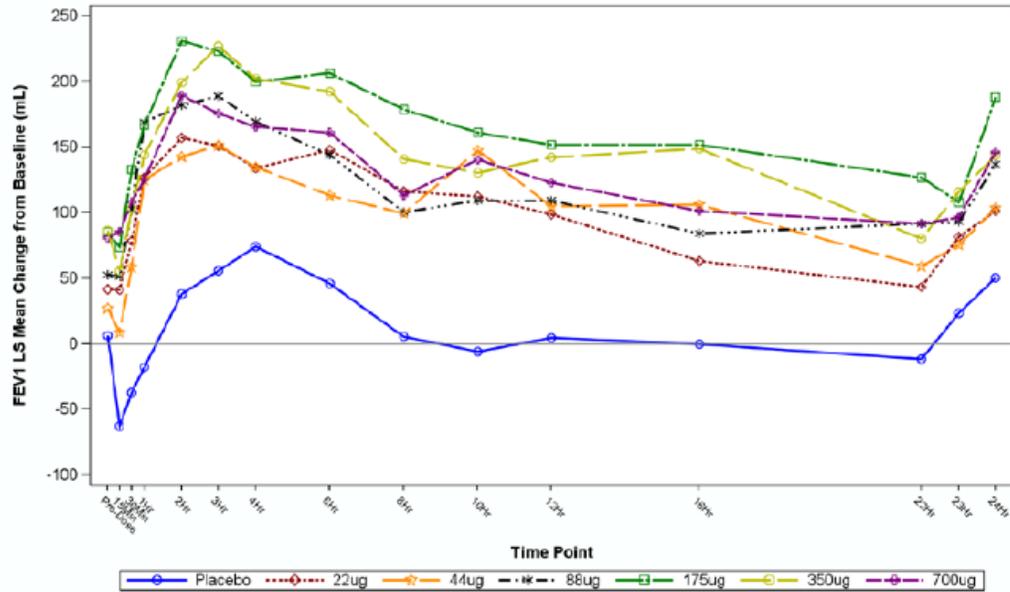
Study 91 was a phase 2, randomized, double-blind, multiple-dose, incomplete-block, crossover study in patients with moderate-to-severe COPD. The study evaluated REV 22, 44, 88, 175, 350, and 700 mcg given once-daily for 7 days in each of 5 treatment periods. There was a 10- to 16-day washout between periods. The primary endpoint was trough FEV₁ at day 7. The change from baseline in trough FEV₁ for 88 mcg to 700 mcg doses of revefenacin was statistically significant compared to placebo. Numerically, the 175 mcg dose had the largest improvement in trough FEV₁ (Figure 1). Twenty-four-hour serial FEV₁ was also evaluated (Figure 2).

Figure 1: Study 91. Change from baseline in trough FEV₁ difference from placebo, day 7



Source: Study 91 CSR; Figure 2; p. 61

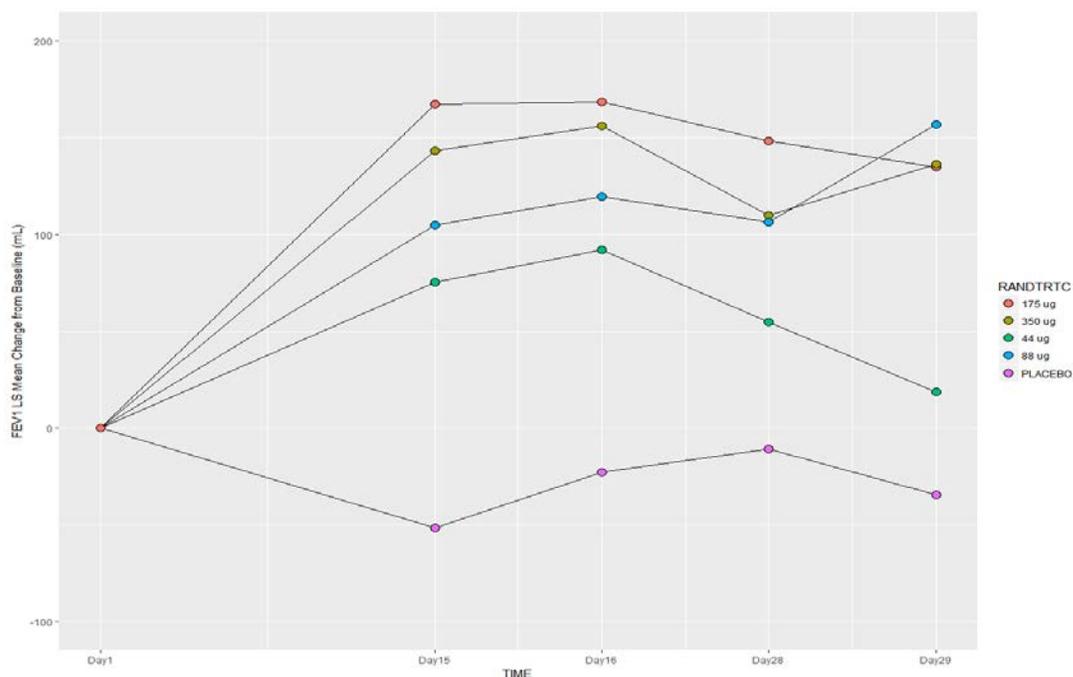
Figure 2. Study 091. Change from baseline in serial FEV₁ over 24 hours on days 7/8



Source: Study 91 CSR; Figure 3; Page 64

An additional study to confirm the dose-response was conducted. Study 117 was a randomized, double-blind, placebo-controlled, parallel group, multicenter study in moderate-to-severe COPD patients. Evaluated REV doses included 44, 88, 175, and 350 mcg given once-daily. The primary efficacy endpoint was the change from baseline in trough FEV₁ on Day 29. Statistically significant differences compared to placebo were observed for doses ≥ 88 mcg (Figure 3). As with Study 91, doses higher than 175 mcg did not appear to result in increased improvements in FEV₁. The results of this study, along with Study 9,1 supported the choice of doses 88 mcg and 175 mcg for the phase 3 studies.

Figure 3: Study 117. Change from baseline, serial trough FEV₁ over days 1-29



Source: Statistical Review; figure 7; page 24

Once-daily and twice-daily dosing regimens were evaluated in Study 116; a randomized, double-blind, placebo-controlled, multiple-dose, 3-period crossover study patients with moderate-to-severe COPD. Treatments groups included REV 44 mcg twice daily, 175 mcg once-daily, and placebo. The primary efficacy endpoint was change from baseline in FEV₁ (0 to 24 hours) on Day 7. REV 44 mcg twice-daily and 175 mcg once-daily demonstrated statistically significant increases in FEV₁ versus placebo. Given the difference in total daily dose, the data from this study are limited to support the once-daily dosing. However, the serial spirometry data support the once-daily dosing.

Overall, results from Studies 91, 116, and 117 support the 88 mcg and 175 mcg once-daily doses included in the phase 3 program.

Confirmatory Studies: Studies 126 and 127

Studies 126 and 127 were 12-week, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of REV 88 mcg and REV 175 mcg administered once-daily via the Pari LC Sprint general use nebulizer in patients with moderate-to-very severe COPD.

Studies 126 and 127 enrolled adult male and female patients ≥ 40 years of age with a clinical diagnosis of moderate-to-very severe COPD according to the GOLD 2011 guidelines. Patients were current or ex-smokers with ≥ 10 pack-year smoking history, with a post-bronchodilator

FEV₁ of < 80% of predicted normal and greater than 0.7 L, an FEV₁/FVC ratio less than 0.70, and had the ability to perform reproducible spirometry according to the ATS/ERS guidelines.

The primary endpoint in both studies was the change from baseline in trough FEV₁ at Week 12. Trough FEV₁ was defined as the mean of the two FEV₁ values obtained at 23.25 hours and 23.75 hours after the day 84 dose.

Baseline demographics were fairly balanced across treatment groups and were generally representative of the population in whom COPD is known to occur. The mean age for the two studies ranged from 63-64 years, with the majority of patients being white (89-91%) males (50-51%) <65 years of age (50-66%). These studies were conducted fully in the United States. Of the study population, 8% to 10% were black patients.

Most patients completed study (77-79%) and treatment (77-79%). The number of patients who discontinued from treatment was also fairly balanced, with higher premature discontinuations in the placebo group. The most common reason for premature discontinuation from the study was adverse events.

Studies 126 and 127 were the primary studies that support the bronchodilator claim for REV. Results from the primary efficacy analysis from these studies showed statistically significant differences between both REV 88 mcg and placebo and REV 175 mcg (Table 2).

Table 2. Primary Efficacy Results. LS Mean Difference in Change From Baseline in Trough FEV₁ (L) at Week 12 (ITT) – Studies 126 and 127

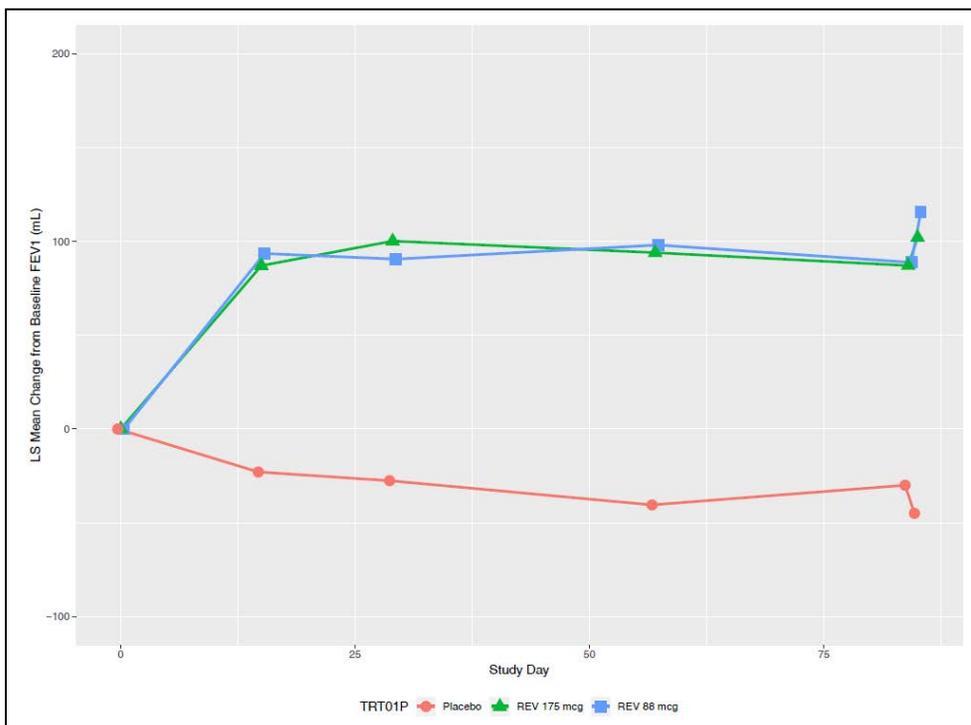
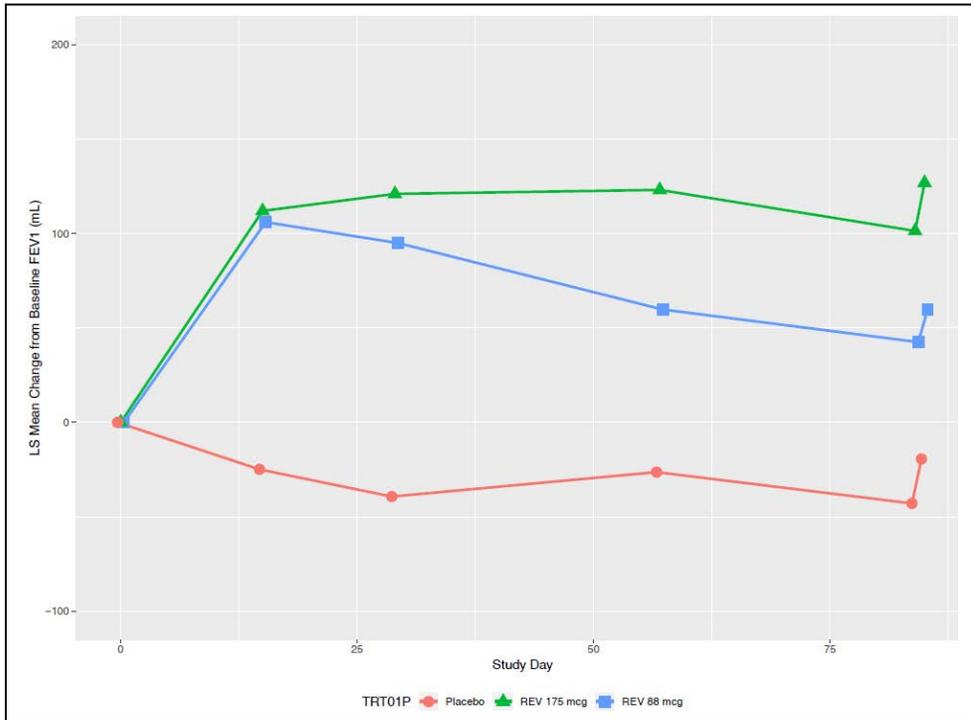
	Study 126			Study 127		
	Placebo N = 209	REV 88 mcg N = 212	REV 175 mcg N = 198	Placebo N = 208	REV 88 mcg N = 205	REV 175 mcg N = 197
CFB trough FEV ₁ LS Mean (SE)	-19.4 (16.1)	59.8 (15.1)	126.8 (15.4)	-44.9 (18.8)	115.6 (18.6)	102.9 (18.5)
LS Mean Difference (SE) from placebo	--	79.2 (21.3)	146.3 (21.6)	--	160.5 (25.5)	147.0 (25.5)
95% CI	--	(37.3, 121.1)	(103.7, 188.8)	--	(110.5, 210.5)	(97.0, 197.1)
Adjusted p-value vs. Placebo		0.0003	< 0.0001		< 0.0001	< 0.0001

REV=revfenacin, CFB = change from baseline; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; ITT = intent to treat; mL = milliliter(s); LS = least squares; SE = standard error
Source: Statistical Review; Table 4.

While both doses demonstrated statistically significant improvements compared to placebo, in Study 127 the FEV₁ effect was numerically similar between the 88 mcg and 175 mcg REV doses. However, in Study 126, consistent with the dose-ranging studies (Figure 3), the FEV₁ effect size for the 175 mcg was numerically larger than the 88 mcg dose. Additionally, in the 52-week safety study (Study 128), which compared REV 88 mcg, REV 175 mcg, and tiotropium; for the exploratory endpoint of FEV₁, the 175 mcg dose had a numerically larger effect size compared to the 88 mcg dose (refer to Statistical Review, Figure 8). FEV₁ time

profile curves for Studies 126 and 127 over the study treatment period also showed consistent efficacy over time. These results were consistent with the primary analysis. The curves for Studies 126 and 127 are shown in Figure 4. These data taken as a whole support the Applicant's selection of the 175 mcg for registration.

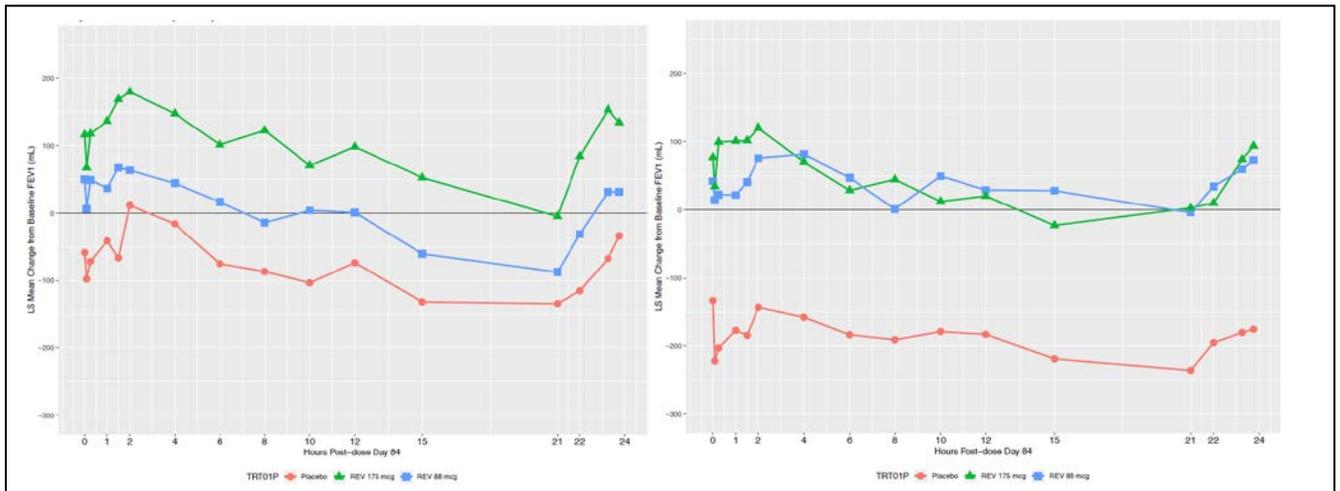
Figure 4. Study 126 and 127. LS Mean Change from Baseline in FEV1 over the 12-week treatment period (upper panel=Study 126, lower panel=Study 127)



Source: Statistical Reviewer

Twenty-four-hour serial spirometry was performed in a subset of patients in both studies. The 24-hour FEV₁ at day 85 are show in Figure 5. As in the primary analysis, in Study 126, the higher REV dose demonstrated a larger FEV₁ treatment effect versus the lower dose. In Study 127, FEV₁ treatment effect appeared similar between doses.

Figure 5. Study 126 and 127. Twenty-four (24) Hour Serial Spirometry at Day 84/85 [LS Mean Change from Baseline in FEV₁ (left panel=Study 126, right panel=Study 127)]



Source: Statistical Reviewer

Subgroup analyses of the primary endpoints were conducted by gender, age, race, airflow limitation, smoking status, ICS use, LABA/ICS or LABA use, and reversibility. In general, the subgroup analyses were consistent with the primary results from the overall population.

The St. George's Respiratory Questionnaire (SGRQ) is a patient-reported outcome instrument which measures symptoms, activities, and the impact of disease on daily life in patients with COPD. The minimal clinical important difference (MCID) for the SGRQ has been determined to be 4 points for COPD patients. The SGRQ was assessed as a secondary endpoint in both studies 126 and 127. In Study 126, the SGRQ responder rate for the REV 88 mcg, REV 175 mcg, and placebo were 47.3%, 48.9%, and 33.8%, respectively. The odds ratio for the REV 175 mcg dose compare to placebo was 2.1 with a 95% confidence interval of (1.1, 3.8). In Study 127, similar trends were observed, though the 95% confidence interval for the odds ratios did not exclude 1. The SGRQ responder rate for the REV 88 mcg, REV 175 mcg, and placebo were 46.2%, 45.0%, and 38.6%, respectively. The odds ratio for the REV 175 mcg dose compare to placebo was 1.3 with a 95% confidence interval of (0.7, 2.4). These are shown in Table 3.

Table 3. St. George’s Respiratory Questionnaire Responder Analysis – Studies 126 and 127

	Study 0126			Study 0127		
	Placebo N = 209	REV 88 mcg N = 212	REV 175 mcg N = 198	Placebo N = 208	REV 88 mcg N = 205	REV 175 mcg N = 197
Responders, n (%)	46 (33.8)	70 (47.3)	68 (48.9)	54 (38.6)	67 (46.2)	67 (45.0)
Odds Ratio (95% CI)	-	2.1 (1.1, 3.8)	2.1 (1.1, 3.9)	-	1.4 (0.8, 2.5)	1.3 (0.7, 2.4)
Responder defined as a decrease in 4 points in SGRQ						
Source: Clinical Review; Table 12						

Efficacy Conclusions

The Applicant provides support for the efficacy of REV 175 mcg once-daily for the maintenance treatment of COPD by demonstrating a statistically significant improvement in lung function in terms of change from baseline in trough FEV₁ compared to placebo in two replicate 12-week studies. The efficacy of REV 175 mcg once-daily was also supported by health-related quality of life, as measured by the SGRQ.

The clinical and statistical review teams are in agreement that the data provided are adequate to support the efficacy of REV 175 mcg for the treatment of patients with COPD. I agree with this conclusion.

7. Safety

The safety evaluation of REV relies primarily on 3-month data from placebo-controlled Studies 126 and 127. Pooling of data across the Studies 126 and 127 to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and doses of REV received (88 mcg and 175 mcg once daily). Safety assessments included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long-term, open-label, active-controlled (tiotropium) safety study (Study 128) was conducted and did not reveal any additional safety signals.

The 3-month safety database included 1,263 COPD patients; 417 treated with REV 88 mcg once daily, 395 patients treated with REV 175 mcg once daily, and 418 patients treated with placebo.

As previously discussed, approximately 20% of patients discontinued treatment prematurely. Study drug withdrawal occurred more frequently in the placebo (26%) group compared to REV 88 mcg (21%) and 175 mcg (18%) groups. The most common AE leading to discontinuation were events occurring in the respiratory, mediastinal, and thoracic system organ class (SOC). The most common preferred term was COPD exacerbation. Adverse events leading to discontinuation occurred more commonly in placebo versus REV-treated patients. Death was a rare occurrence, with one event (murder by stepson) occurring in the

REV 175 mcg group and one event in the placebo group. The overall occurrence of SAEs was low and fairly balanced across REV 88 mcg, REV 175 mcg, and placebo treatment groups [n=26 (6%), n=20 (5%), and n=26 (6%), respectively]. In general, the numbers of patients experiencing individual SAEs were small, and without meaningful imbalances.

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs which included anticholinergic effects, cardiovascular events, gastrointestinal obstruction, and adjudicated major adverse cardiovascular events (MACE). As expected, anticholinergic events (e.g. dry mouth, dizziness, constipation) were reported somewhat more frequently in the REV treatment arms compared to the placebo arms. The most frequently reported anticholinergic AE was dizziness [n=4 (0.9%) in the placebo group, n=6 (1.4%) in the REV 88 mcg group, and n=7 (1.7%) in the REV 175 mcg group]. Cardiovascular events of special interest were generally similar across placebo, REV 88 mcg, and REV 175 mcg groups [(n=8 (1.9%), n=10 (2.4%), n=10 (2.5%), respectively]. Adjudicated MACE was rare and reported in 5 patients, two in the REV 88 mcg group, two in the REV 175 mcg group, and 1 in the placebo group. Gastrointestinal obstruction AEs were also rare occurring in one patient in the REV 88 mcg group. Overall, while there were some numerical differences, these differences were small and not clinically meaningful.

Adverse events were generally balanced between the REV and placebo groups. Common adverse events occurring in $\geq 2\%$ of patients and more commonly in REV groups versus placebo included cough, oropharyngeal pain, upper respiratory tract infection, nasopharyngitis, urinary tract infection, headache, and back pain.

Similar analyses were performed in the long-term safety study, Study 128, and the findings were consistent with the results seen for the primary 3-month safety database.

Safety Conclusions

In summary, the safety data for the REV development program in COPD did not reveal any new safety concerns. The adverse event observed were generally those observed in patients with COPD and with similar approved anticholinergic products. The safety of REV 175 mcg is supported. The clinical team has concluded that the data provided are adequate to support the safety of REV 175 mcg for the treatment of patients with COPD. I agree with this conclusion.

8. Advisory Committee Meeting

A Pulmonary Allergy Drug Advisory Committee (PADAC) meeting was neither convened nor required for this submission as the safety and efficacy of an anticholinergic such as REV in the treatment of COPD is well-described and well-understood.

9. Pediatrics

Theravance is requesting an indication for COPD. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required. The PeRC had previously agreed that

for such COPD applications, a full waiver will be granted because studies would be impossible or highly impracticable, since the disease entity of COPD does not exist in pediatric patients.

10. Other Relevant Regulatory Issues

- Financial Disclosure: Appropriate financial disclosure information was provided by the Applicant. None of the investigators reported disclosable financial interests.
- Inspections:
 1. OSI inspection was conducted for three investigator sites. At one site (38705), the inspector noted two protocol violations/deviations, but did not think that they would affect the overall analysis. As a result, voluntary action was indicated. The two other sites were classified as no action indicated.
 2. OSIS inspection was conducted for the bioanalytical site (b) (4). No objectionable conditions were observed and a Form FDA 483 was not issued.
 3. CMC pre-approval inspection was conducted at the drug product manufacturing site (b) (4). After the inspection, an FDA Form 483 was not issued. (b) (4) met all pre-approval inspection objectives, and the inspection was classified no action indicated.

11. Labeling

The name tradename Yupelri was determined to be acceptable. The labeling was reviewed by various disciplines within DPARP as well as consulting groups (OPDP, DMPP, DMEPA). Labeling has been agreed upon with the sponsor.

The sponsor proposed the following indication for revefenacin – (b) (4) maintenance treatment of (b) (4) patients with COPD, (b) (4). (b) (4) This is consistent with the indication for similar inhalation products. In July 2018, FDA issued a Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format. During review of this application, the Division re-evaluated the approach to the indication statement for inhaled products for the treatment of COPD and determined that a revised indication statement is more consistent with the concepts outlined in the Guidance. The following were key considerations in the revised indication statement:

- The Guidance emphasizes that the indication statement should be concise and scientifically accurate. (b) (4)
(b) (4) COPD indication, “treatment of COPD”, is appropriate for inhaled COPD products. This general indication conveys the disease that is being treated (b) (4)
(b) (4) This approach is also consistent with how the

indication is handled for other chronic diseases, such as asthma, rheumatoid arthritis, ulcerative colitis, psoriasis, etc.

- While the indication for inhalation products has typically included the posology - once or twice daily, this information does not belong in the indication statement. The Dosage and Administration section provides this information.



Going forward, the indication statement for the inhaled COPD products will be more general and read “for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)”. This clear and concise indication is consistent with the most current approach described in *Guidance to Industry: Indication and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM612697.pdf>).

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

- Other Postmarketing Requirements and Commitments

There are no Postmarketing requirements or commitments.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY M SEYMOUR
11/01/2018

MARY T THANH HAI
11/01/2018
Concur with Dr. Seymour's conclusions and recommendation