

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210598Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

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| <b>Date</b>  | October 2, 2018  |
| <b>From</b>  | Robert H Lim, MD   |
| <b>Subject</b>                                     | Cross-Discipline Team Leader Review  |
| <b>NDA/BLA #</b>                                   | NDA 210598   |
| <b>Supplement#</b>                                 |  |
| <b>Applicant</b>                                   | Theravance   |
| <b>Date of Submission</b>                          | November 13, 2017  |
| <b>PDUFA Goal Date</b>                             | November 13, 2018  |
| <b>Proprietary Name / Established (USAN) names</b> | Yupelri/revefenacin inhalation solution  |
| <b>Dosage forms / Strength</b>                     | 175 mcg inhalation solution  |
| <b>Proposed Indication(s)</b>                      | Treatment (b) (4) of patients with chronic obstructive pulmonary disease (COPD)                  |
| <b>Recommended:</b>                                | Approval for the (b) (4) treatment of patients with chronic obstructive pulmonary disease (COPD) |

### 1. Introduction

Theravance submitted a 505(b)(1) New Drug Application (NDA) 210598 on November 13, 2017, for revefenacin inhalation solution (REV, proprietary name Yupelri inhalation solution) indicated for the (b) (4) maintenance treatment of (b) (4) patients with chronic obstructive pulmonary disease (COPD). REV is a long-acting anticholinergic and is formulated as a solution for inhalation within a unit-dose vial to be delivered via a general use nebulizer. The unit-dose, single use vial will contain 175 mcg of REV in 3 mL. The proposed dose is one vial (175 mcg) by inhalation (b) (4)

To support the REV 175 mcg once daily (qD) dose for COPD, Theravance has conducted a clinical program that includes multiple dose-ranging trials, two confirmatory phase 3 clinical trials, and one long-term safety trial. This memo provides an overview of the application, with a focus on the clinical data which demonstrate the efficacy and safety of REV 175 mcg qD in patients with COPD. Focus is placed on the trough FEV<sub>1</sub> (lung function), which was the primary endpoint in the lung function studies designed to demonstrate efficacy. This memo also addresses the recommendations from each of the individual review disciplines and consultants.

### 2. Background

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 and long-acting anticholinergics; combination products containing long-acting beta-2 adrenergic agonists and corticosteroids; combination products containing long-acting beta-2 adrenergic agonists, corticosteroids, and long-acting anticholinergic; products containing methylxanthines; and

phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), 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 long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler, Spiriva Respimat), aclidinium bromide (Tudorza Pressair), glycopyrrolate (Lonhala Magnair, Seebri 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.<sup>1</sup> These concerns have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat.<sup>2, 3</sup> Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in a COPD program to limit high systemic exposure and potential safety concerns.

### **Relevant Regulatory History for REV**

Revefenacin was studied under IND 119840, opened on February 21, 2014. Relevant regulatory interactions are summarized below:

#### **Pre-IND Meeting 12-12-13**

- Advised to submit a safety database that includes patients in Phase 3 trials that are representative of target population.
- Advised to obtain 24-hour FEV1 time profiles after initial dosing and at end of study; a subset of 30-40 patients/arm was felt to be acceptable.
- Inclusion of an active comparator as a benchmark was recommended.
- Recommended using the same type of 510K cleared general purpose nebulizer/compressor in all studies.

#### **EOP2 meeting 12-8-14**

- (b) (4) 88mcg and 175 mcg once daily to carry forward into phase 3 were found

<sup>1</sup> FDA Early Communication about Ongoing Safety Review of Tiotropium. [http://www.fda.gov/cder/drug/early\\_comm/tiotropium.htm](http://www.fda.gov/cder/drug/early_comm/tiotropium.htm)

<sup>2</sup> 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.

<sup>3</sup> 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.

reasonable.

- Recommended broadening cardiovascular exclusion criteria to allow for a study population more reflective of the target population.
- The FDA agreed to open label tiotropium in the long term safety study.

#### Pre-NDA Meeting 3-16-17

- Efficacy and safety data generated from studies 126, 127 and 128 were adequate for review

### **3. CMC/Device**

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

The drug product (REV) is proposed to be delivered via a 510K cleared general use nebulizer.

#### **Drug Product and Drug Substance**

Revefenacin, the active component of Yupelri Inhalation Solution, 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 substance is a white to off-white, achiral, crystalline powder. The selected anhydrous crystal form of Revefenacin (Form 1) is the most thermodynamically stable form. (b) (4)

(b) (4) However, the drug substance has been consistently produced as the thermodynamically favorable Form 1.

The drug product is formulated with compendial grade excipients, (b) (4)

(b) (4) The drug product formulation is an isotonic, sterile aqueous solution containing sodium chloride, citric acid, and sodium citrate, at pH 5.0. Standard (b) (4) (b) (4) is used to package the solution formulation and the control strategy for leachables from the container (low density polyethylene or LDPE) and foil (b) (4) overwrap was found to be adequate, considering the extractables and leachables data provided. The stability for the drug product support a 24-month shelf-life.

Inhalation solutions are required to be sterile, thus it is important that the applicant performs 100% leak testing on filled vials, and the associated validation of the test was found to be acceptable. Environmental monitoring (b) (4) testing being performed were found to be acceptable as well. (b) (4)

(b) (4) Finally, 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) (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) (b) (4). The site is also recommended as adequate for the operations outlined in NDA 210598.

## 4. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. The Applicant has performed a complete nonclinical program for REV. There are no outstanding nonclinical issues. The nonclinical program is summarized below.

Pharmacology: 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.

Revefenacin forms a carboxylic acid metabolite, THRX-195518, by amide hydrolysis. THRX-195518 constitutes approximately 76% of total systemic exposure in COPD patients at steady-state. Pharmacology studies demonstrated that THRX-195518 is active and has affinity for all five human muscarinic receptor subtypes. Based on competition binding assays, THRX-195518 has 3-fold to 10-fold less binding affinity than revefenacin for the muscarinic receptor subtypes. The 3-fold to 10-fold reduced binding affinity of metabolite THRX-195518 compared to revefenacin was not considered biologically significant based upon the variability observed in these studies.

There was limited data to assess the functional antimuscarinic activity of metabolite THRX-195518 and the comparable activity of the metabolite relative to revefenacin. It was concluded that metabolite THRX-195518 could contribute to potential systemic antimuscarinic pharmacodynamic activity of revefenacin. As such, THRX-195518 is considered an active metabolite.

ADME: Revefenacin contains a primary amide group that undergoes amide hydrolysis to form the carboxylic acid metabolite, THRX-195518. This reaction can be mediated by amidases. In *in vitro* studies using human, rat, dog, rabbit, and mouse hepatocytes, the major route of metabolism of revefenacin was hydrolysis of the primary amide to form a carboxylic acid metabolite, THRX-195518. Metabolic profiles were generally qualitatively similar between humans and nonclinical species. THRX-195518 was more stable than revefenacin in hepatocytes from all species tested. No detectable metabolism of revefenacin was observed in human lung preparations (microsomes and S9 fractions). In *in vivo* nonclinical studies with rats, dogs, mice, and rabbits that received revefenacin by various routes (inhalation, oral, subcutaneous, intravenous), THRX-195518 constituted greater than 10% of systemic exposure. In COPD patients, following inhaled administration of revefenacin, metabolism to THRX-195518 occurred rapidly and plasma exposures to THRX-195518 exceeded those of revefenacin by approximately 4- to 6-fold (based on AUC), suggesting extensive conversion of revefenacin to THRX-195518. In healthy subjects, conversion of revefenacin to THRX-195518 was also rapid after inhaled administration; however, plasma exposure (AUC) was lower, averaging approximately 30% to 98% of revefenacin exposure. Nonclinical toxicology studies provide adequate safety margins for clinical exposures to revefenacin and THRX-195518 as discussed below.

Toxicology: Chronic inhalation toxicology studies with revefenacin were conducted in rats (26 weeks) and dogs (39 weeks). There were no treatment-related deaths in either study. Pharmacodynamic effects were observed in dogs that consisted of increased heart rate, which was associated with decreases of the RR, PR, and QT intervals, and decreased tear production. The cardiac effects in dogs were considered potentially 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 and metabolite THRX-195518 in rats constituted about 76% and 24% of total systemic exposure, respectively. Revefenacin and metabolite THRX-195518, in dogs constituted about 35% and 65% of total systemic exposure, respectively. Exposures to revefenacin and metabolite, THRX-195518, in rats and dogs provided adequate safety margins ( $\geq 1$ ) for human exposures at the clinical dose of 175  $\mu\text{g}$  QD.

Genetic toxicity and Carcinogenicity: 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.

Reproductive Toxicity: The Applicant 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.

Safety Evaluation of Impurities: Specified drug substance impurities and/or degradants included [REDACTED] (b) (4) Levels of the 5 specified impurities were judged to be qualified with respect to safety based on the nonclinical studies. Levels of organic impurities with structural alerts [REDACTED] (b) (4) and inorganic/elemental impurities were also reviewed and no safety issues were identified as levels of these compounds and elements were low. Based on review of extractables and leachables studies conducted with the container closure system at the time of this review; there are no safety issues.

## 5. Clinical Pharmacology/Biopharmaceutics

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

The clinical pharmacology (CP) program for revefenacin solution for inhalation included a first-in-human, single ascending dose study (AC5108696), a mass-balance study (130), a hepatic impairment study (134; reduced study design), a renal impairment study (135; reduced study design), and a thorough QT study (136) in healthy subjects. The pharmacokinetic (PK) profile of revefenacin was also evaluated in randomized, double-blind, crossover, single-dose (59) and repeat-dose (91) studies in COPD patients, and a randomized, double-blind, parallel-group, repeat-dose study in COPD patients (117). Sparse sampling PK data was collected in two randomized, double-blind, placebo-controlled, multiple-dose, parallel-group replicate 3-month studies (126 and 127) in COPD patients. The program was also supported by results from 19 in vitro human biomaterial studies. The dose-ranging studies will be discussed in more detail in the clinical efficacy section.

The following are the major findings from the current review:

- 1) 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 THR-195518. There was a 1.2 to 2.3-fold increase in AUC of revefenacin; THR-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.
- 2) 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 THR-195518. There was a 1.2-fold increase in AUC of revefenacin; the THR-195518 exposure (AUC) was increased by 2.8 to 4.7-fold. Given this increased exposure to the active metabolite (THR-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.
- 3) Following administration of revefenacin inhalation solution by nebulization in healthy subjects or COPD patients,  $C_{max}$  of revefenacin and THR-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 (THR-195518) following once-daily dosing in COPD patients is 22 to 70 hours.
- 4) There is minimal renal excretion (<1%) of revefenacin and THR-195518 following inhaled administration of revefenacin. These results indicate extensive hepatobiliary elimination of revefenacin and THR-195518.

- 5) 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).
- 6) The mean THRX-195518  $C_{max}$  and  $AUC_6$  values were approximately 2.4- and 2.2-fold higher, respectively, in COPD patients as compared to healthy subjects.
- 7) Revefenacin was actively transported by efflux transporters P-gp and BCRP with the highest net efflux ratio of 18 and 17.5, respectively. Hence, revefenacin is a substrate of P-gp and BCRP.
- 8) THRX-195518 showed transporter-specific accumulation in both OATP1B1- and OATP1B3-expressing cells (12.8-fold and 5.8-fold accumulation compared to control cells, respectively) suggesting that THRX-195518 is a substrate for both transporters.
- 9) No significant CYP-mediated inhibition of CYP1A2, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 or induction of CYP1A2, CYP2B6, or CYP3A4/5 was observed for revefenacin or THRX-195518.
- 10) Neither age, body weight, sex or creatinine clearance had relevant effects on drug exposure.

The above findings were based on CP data from the phase 1 and 2 studies. CP data from the phase 3 studies were not considered. 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. An IR was sent asking the Applicant to provide an explanation for these findings. The Applicant attributed the issue to 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 is retained on the clothing and transferred to tubes]. On inspection of the clinical sites, one site used 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 was deemed not reliable and were not used in CP analyses.

## 6. Clinical Microbiology

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

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.

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

Abbreviations: INH- inhalation, R- randomized, DB- double-blinded, PC- placebo-controlled, PG- parallel group, AC/OL- active comparator open-label, CO-cross-over

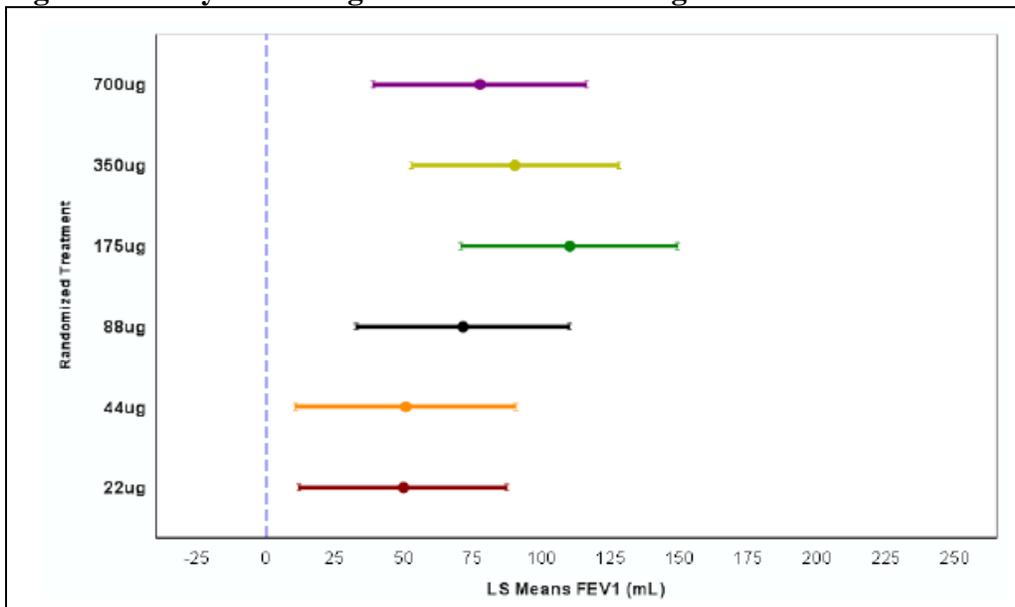
\* Two sites excluded from efficacy analysis due to site misconduct found on sponsor's internal audit

**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.

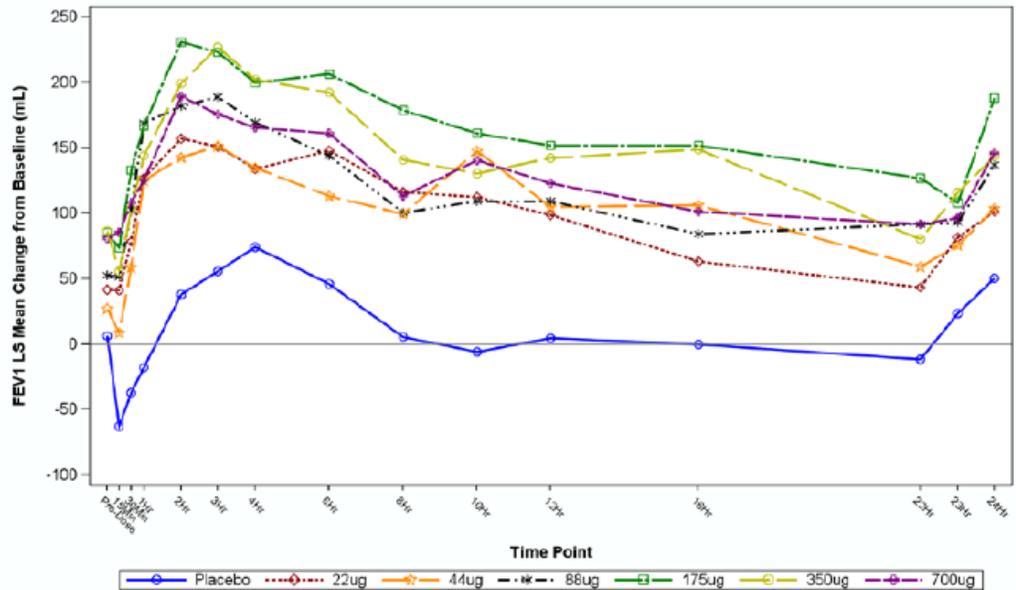
Study 091 was a phase 2, randomized, double-blind, multiple-dose, incomplete-block, crossover study in patients with moderate to severe COPD. The study evaluated REV 22, 44, 88, 175, 350, and 700mcg given once daily for 7 days in each of 5 treatment periods. There was a 10- to 16-day washout between 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

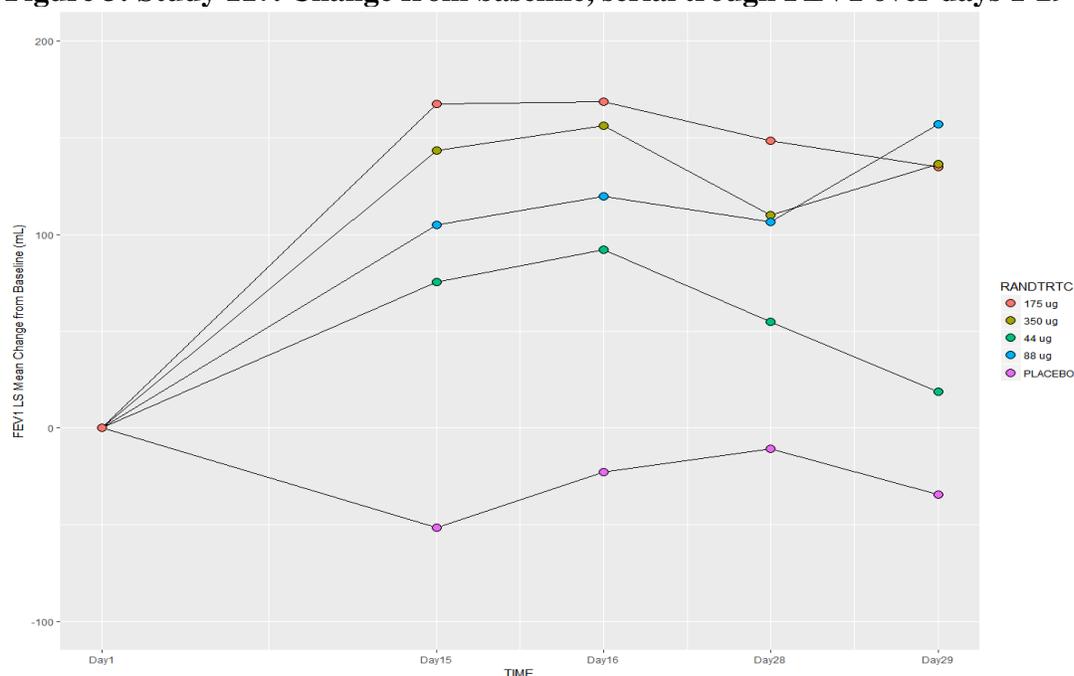
**Figure 2. Study 091. Change from Baseline in Serial FEV1 Over 24 hrs on Days 7/8**



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 350mcg 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  $\geq 88$ mcg (Figure 3). As with Study 91, doses higher than 175mcg did not appear to result in increased improvements in FEV1. The results of this study along with Study 91 supported the choice of doses 88 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. Once-daily dosing of REV 175 mcg was numerically greater than twice-daily dosing of REV 44 mcg, thereby demonstrating that the lower daily dose in divided intervals did not provide greater efficacy in terms of lung function than a higher once-daily dose. This, along with the serial spirometry data support once daily dosing.

Overall, results from Studies 91, 116, and 117 support the 88 mcg and 175mcg 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  $\geq 40$  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  $\geq 10$  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 FEV<sub>1</sub> at Week 12. Trough FEV<sub>1</sub> was defined as the mean of the two FEV<sub>1</sub> 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 FEV<sub>1</sub> (L) at Week 12 (ITT) – Studies 126 and 127**

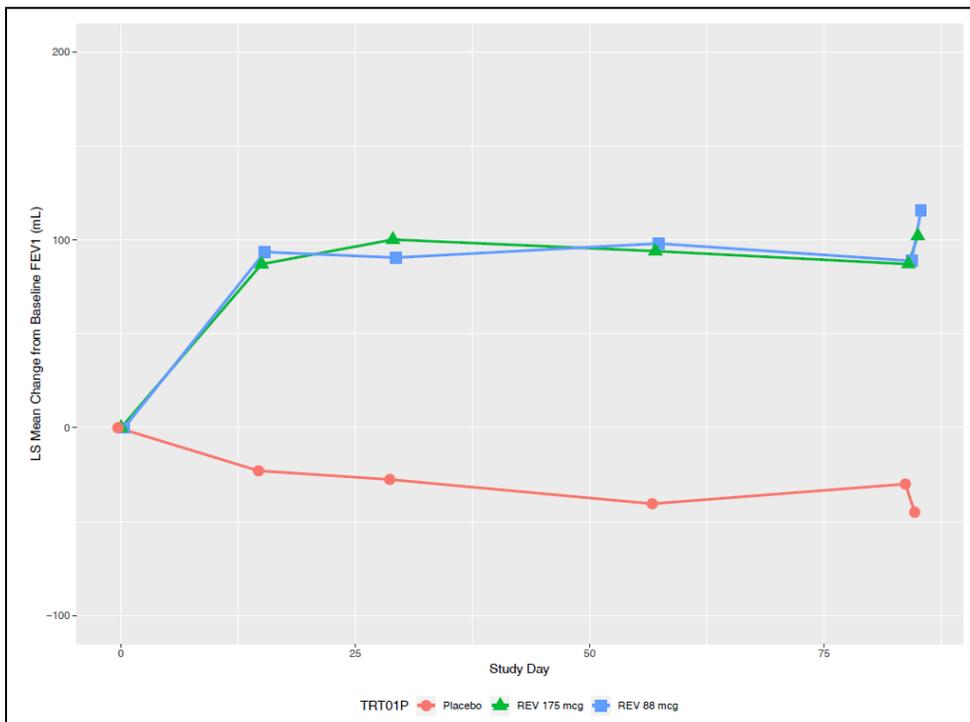
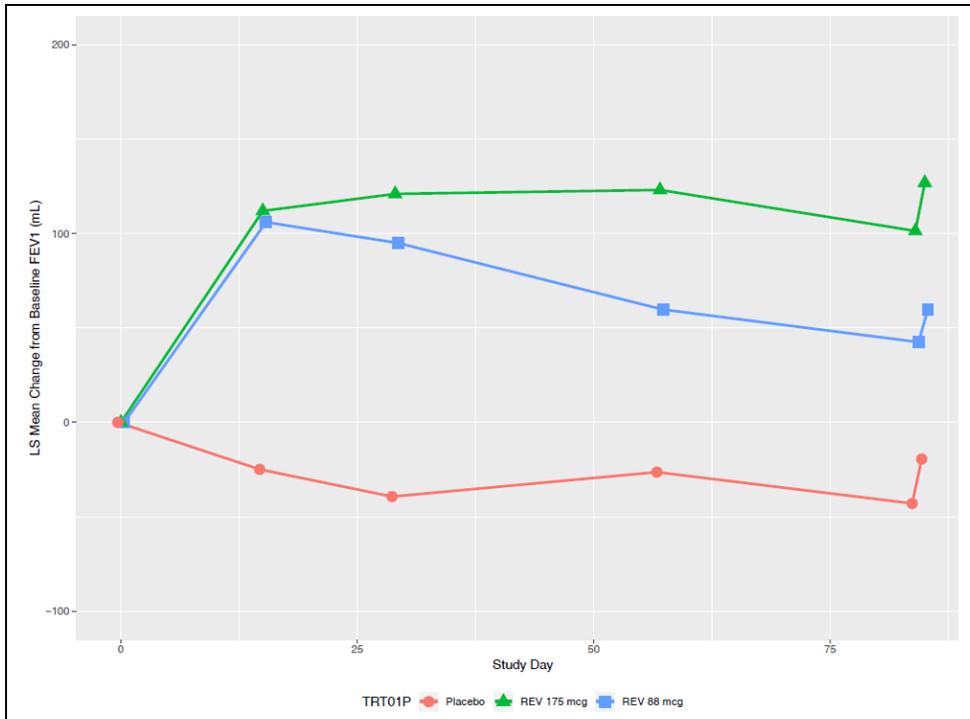
|                                      | Study 126          |                          |                           | Study 127          |                          |                           |
|--------------------------------------|--------------------|--------------------------|---------------------------|--------------------|--------------------------|---------------------------|
|                                      | Placebo<br>N = 209 | REV<br>88 mcg<br>N = 212 | REV<br>175 mcg<br>N = 198 | Placebo<br>N = 208 | REV<br>88 mcg<br>N = 205 | REV<br>175 mcg<br>N = 197 |
| CFB trough FEV1 LS Mean (SE)         | -19.4<br>(16.1)    | 59.8<br>(15.1)           | 126.8<br>(15.4)           | -44.9<br>(18.8)    | 115.6<br>(18.6)          | 102.9<br>(18.5)           |
| LS Mean Difference (SE) from placebo | --                 | 79.2 (21.3)              | 146.3 (21.6)              | --                 | 160.5<br>(25.5)          | 147.0<br>(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=revefenacin, 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). FEV<sub>1</sub> 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 Applicants selection of the 175 mcg for registration.

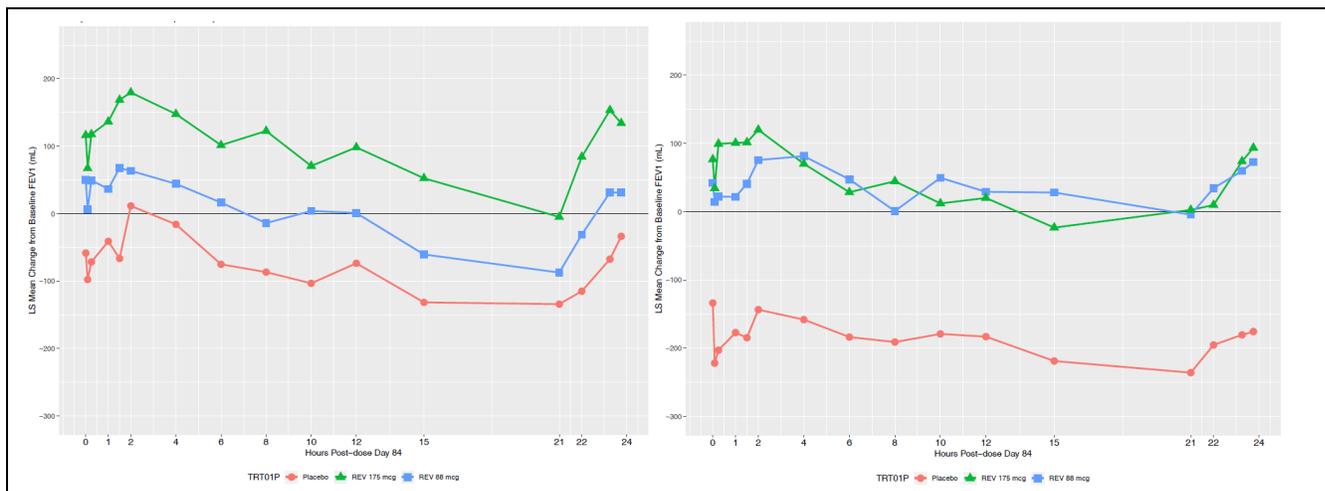
**Figure 4. Study 126 and 127. LS Mean Change from Baseline in FEV1 over the 12-week treatment period (upper panel=Study 126, lower panel=Study 127)**



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 on 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 summarized in shown in Table 3.

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

|  | Study 0126         |                          |                           | Study 0127        |                          |                           |
|--|--------------------|--------------------------|---------------------------|-------------------|--------------------------|---------------------------|
|  | Placebo<br>N = 209 | REV<br>88 mcg<br>N = 212 | REV<br>175 mcg<br>N = 198 | Placebo<br>N =208 | REV<br>88 mcg<br>N = 205 | REV<br>175 mcg<br>N = 197 |
| Responders, n (%)  | 46 (33.8)          | 70 (47.3)                | 68 (48.9)                 | 54 (38.6)         | 67 (46.2)                | 67 (45.0)                 |
| Odds Ratio<br>(95% CI)   | -                  | 2.1<br>(1.1, 3.8)        | 2.1<br>(1.1, 3.9)         | -                 | 1.4<br>(0.8, 2.5)        | 1.3<br>(0.7,2.4)          |
| Responder defined as a decrease in 4 points in SGRQ<br>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 FEV<sub>1</sub> 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.

## **8. 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.

## **9. 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.

## **10. 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 should be granted because studies would be impossible or highly impracticable, since the disease entity of COPD does not exist in pediatric patients.

## 11. 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.

## 12. Labeling

- **Proprietary Name:** The name Yupelri was determined to be acceptable.
- **Physician Labeling:** The label was reviewed by various disciplines within DPARP and the patient labeling team (OPDP and DMPP). Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. Labeling negotiations are ongoing at the time of this review.
- **Medication Guide and Instructions for Use:** These documents were reviewed by the various disciplines in DPARP and the patient labeling team. Multiple changes were made to better convey product information to the patient. Negotiations are ongoing at the time of this review.
- **Carton and Immediate Container Label:** These were reviewed by various disciplines of the Division and DMEPA. Negotiations are ongoing at the time of this review.

## 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval for Yupelri inhalation solution 175mcg once daily for the treatment of patients with COPD, pending agreement with labeling.

- **Risk Benefit Assessment**

The overall risk benefit assessment supports the approval of REV 175 mcg once daily for the treatment of patients with COPD. Efficacy was confirmed in two identical replicate phase 3 twelve week treatment period studies in moderate to very severe COPD patients (Studies 126 and

127). Results from both studies demonstrated that once daily treatment with REV 175 mcg administered via a general use nebulizer resulted in significant improvements in trough FEV1. This effect was consistent over the treatment period. Additionally, SGRQ data was supportive of a treatment benefit. Review of the safety data from these two studies, as well as the long-term safety study (Study 128) did not reveal significant safety concerns and the safety profile was consistent with those observed for other anticholinergic products.

(b) (4)

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

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

- **Recommendation for other Postmarketing Requirements and Commitments**

None.

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/s/  
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ROBERT H LIM  
10/02/2018