CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208294Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208294	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Bevespi Aerosphere Established/Proper Name: Glycopyrrolate and formoterol fumarate Dosage Form: MDI Strengths: 9/4.8 mcg		
Applicant: Pearl Therapeutics		
Date of Receipt: 06/25/2015		
PDUFA Goal Date: 04/25/2016	Action Goal Date (if different):	
RPM: Brandi Wheeler		
Proposed Indication(s): COPD		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug, by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Literature	Warnings and Precautions, Section 5.11 Renal Impairment, Section 8.6 Hepatic Impairment, 8.7 Renal Impairment Clinical Pharmacology, Section 12.1 MOA, Section 12.3 PK
NDA 17558 Robinul Injection	Warnings and Precautions, Section 5.11 Renal Impairment, Section 8.1 Pregnancy Clinical Pharmacology, Section 12.3 PK Nonclinical Toxicology, Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Pearl is using the 505(b)(2) pathway in order to rely on the Agency's previous finding of safety for glycopyrrolate including pharmacokinetic (PK) and nonclinical data from studies conducted with the reference listed drug Robinul® Injection (NDA 017558) and published literature on the PK and pharmacology of glycopyrrolate. The Agency agreed that a relative bioavailability assessment for glycopyrrolate was not needed to support a 505(b)(2) application because there were large exposure margins between Bevespi Aerosphere and Robinul Injection.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Robinul Injection	17558	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Robinul Injection

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form from injection to MDI and for a new indication, COPD.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRANDI E WHEELER
04/25/2016

CLINICAL INSPECTION SUMMARY ADDENDUM

Date	February 26, 2016
From	Anthony Orencia M.D., F.A.C.P., Janice Pohlman M.D., M.P.H.
To	Stacy Chin M.D., Anthony Durmowicz M.D., Brandi Wheeler Pharm.D.
NDA	208294
Applicant	Pearl Therapeutics, Inc.
Drug	Glycopyrrolate-formoterol
NME	No
Therapeutic Classification	Long acting β-agonist (LABA) and long-acting muscarinic antagonist (LAMA)
Proposed Indication	(b) (4) COPD
Consultation Request Date	September 1, 2015
Summary Goal Date	March 25, 2016
Action Goal Date	April 25, 2016
PDUFA Date	April 26, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In summary, three clinical studies were submitted in support of the applicant's NDA. Three clinical sites (Drs. Cifuentes, Mirkil and Garver) were selected for audit.

Based on the inspection of three clinical sites and the sponsor, the data reported to the sponsor by these clinical sites and subsequently by the sponsor to the NDA appear to be reliable and may be used in support of the requested indication. The sponsor's oversight of the studies also appears to be adequate.

The preliminary classification for the inspections of Drs. Cifuentes, Mirkil, and Garver, Jr. is No Action Indicated (NAI). The final classification for the sponsor inspection is Voluntary Action Indicated (VAI). Data submitted by the inspected sites appear acceptable and reliable in support of this specific indication. The anonymous complaints and allegations at the sponsor, Drs. Cifuentes and Mirkil study sites were not substantiated during the inspections.

Observations noted above for the three clinical investigator sites are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. BACKGROUND

Glycopyrronium is a long acting muscarinic antagonist (LAMA) which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Formoterol fumarate is a long acting beta agonist (LABA). As a bronchodilator, formoterol fumarate stimulates β2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation.

Three clinical trials were submitted in support of the applicant's NDA 208294, and selected by DPARP for clinical site inspections. In general, these sites enrolled large numbers of subjects and the groups potentially had differential efficacy findings. Additionally, complaints about two of the three clinical investigators (Drs. Cifuentes and Mirkil) and sponsor were received by the Agency.

Study PT003006
Study PT003-006 was a multicenter, randomized, double-blind, parallel group, chronic dosing (24 weeks), placebo- and active-controlled study to assess the efficacy and safety of treatment with glycopyrronium and formoterol fumarate metered dose inhaler (MDI) (GFF MDI, 14.4/9.6 µg ex-actuator, BID), formoterol fumarate MDI (FF MDI, 9.6 µg ex-actuator, BID), glycopyrronium MDI (GP MDI, 14.4 µg ex-actuator, BID), and tiotropium [Spiriva® (18 µg, open-label, QD)] compared with each other and placebo MDI in subjects with moderate to very severe COPD. The primary objective was to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough forced expiratory volume in 1 second (FEV1) in subjects with moderate to very severe COPD. For U.S. studies, the primary study efficacy endpoint was the change from baseline in morning pre-dose trough FEV1 at Week #24.

Subjects were screened at 160 sites in the USA, Australia, and New Zealand, The first subject enrolled on Jun 6, 2013 and the last subject completed on Feb 19, 2015. A total of 2054 subjects were planned. A total of 2103 subjects were randomized, of which 2100 subjects were analyzed for safety and 2096 subjects were analyzed for efficacy. Per sponsor's interpretation, efficacy of glycopyrrolate-formoterol fumarate MDI 14.4/9.6 µg, glycopyrrolate MDI 14.4 µg, and formoterol fumarate MDI 9.6 µg as twice-daily treatments for COPD over placebo was demonstrated, using trough forced expiratory volume in 1 second (FEV1) in subjects with moderate to very severe COPD.

Study PT003007
Study PT003007 was a multicenter, randomized, double-blind, parallel group, chronic dosing (24 weeks), placebo-controlled study to assess the efficacy and safety of treatment with glycopyrronium and formoterol fumarate metered dose inhaler (MDI) (GFF MDI, 14.4/9.6 µg ex-actuator, BID), formoterol fumarate MDI (FF MDI, 9.6 µg ex-actuator, BID), and glycopyrronium MDI (GP MDI, 14.4 µg ex-actuator, twice-daily [BID]) compared with each other and with placebo MDI in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD). The primary objective of this study was to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough forced expiratory volume in 1 second (FEV1) in

patients with moderate to severe COPD. The primary endpoint was the change from baseline in morning pre-dose trough FEV1 at Week #24.

PT003007 subjects were screened at 140 sites in the USA. The first subject enrolled on July 9, 2013 and the last subject completed on February 25, 2015. A total of 1614 subjects were planned. A total of 1615 subjects were randomized, of which 1610 subjects were analyzed for safety and 1609 subjects were analyzed for efficacy. Per sponsor's interpretation, efficacy of GFF MDI 14.4/9.6 µg, GP MDI 14.4 µg, and FF MDI 9.6 µg as twice-daily treatments for COPD over placebo was demonstrated, using trough forced expiratory volume in 1 second (FEV1) in subjects with moderate to very severe COPD.

Study PT003008
Study PT003008 was a multi-center, randomized, double-blind, parallel group, chronic dosing, active controlled, 28-week safety extension study of the two pivotal 24-week safety and efficacy studies (Studies PT003006 and PT003007). The primary objective of this Phase 3 study is to evaluate the long-term safety and tolerability of glycopyrronium and formoterol fumarate metered dose inhaler (MDI), glycopyrronium MDI, formoterol fumarate MDI and tiotropium (Spiriva®) in subjects with moderate to very severe COPD over 52 weeks.

Study PT003008 was conducted at 205 sites in the United States, Australia, and New Zealand. The first subject enrolled on November 19, 2013 and the last subject completed on December 26, 2014. A total of 850 subjects were planned. Since this was an extension study, 893 subjects who were treated in Study PT003008 were analyzed for efficacy: 583 subjects from Study PT003006 and 309 subjects from Study PT003007. Per sponsor's interpretation, the results of this 28-week extension study to Studies PT003006 and PT003007 demonstrated consistent efficacy of glycopyrrolate-formoterol fumarate MDI 14.4/9.6 µg, glycopyrrolate MDI 14.4 µg, and formoterol fumarate MDI 9.6 µg administered twice daily in subjects with moderate to very severe COPD over 52 weeks.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
Enrique Cifuentes, M.D. Clinical Research Consortium 2727 W. Baseline Rd., Suite 27 Tempe, AZ 85283	Site 6078 Protocol PT003006 Subjects=56 Site 7447 Protocol PT003007 Subjects=40 Site 6078 Protocol PT003008 Subjects=20	October 19 to 23, 2015	Preliminary: NAI

Name of CI, Address	Site #, Protocol # and # of Subjects	Inspection Date	Classification
V. Jerome Mirkil, M.D. 2110 E. Flamingo, Suite 330 Las Vegas, NV 89119	Site 6079 Protocol PT003006 Subjects=43 Site 7450 Protocol PT003007 Subjects=15 Site 6079 Protocol PT003008 Subjects=16	November 16 to 24, 2015	Preliminary: NAI
Andrew Garver, Jr. M.D. SEC Lung, L.L.C. 822 S. Three Notch St # B Andalusia, AL 36420	Site 6021 Protocol PT003006 Subjects=37	October 5 to 9, 2015	Preliminary: NAI
Pearl Therapeutics, Inc. 280 Headquarters Plaza, East Tower, 2nd Floor Morristown, N.J. 07969	Sponsor: (1) Protocol PT003006/Randomized Subjects =2103 (2) Protocol PT003007/Randomized Subjects=1615 (3) Protocol (Rollover) PT003008 Subjects=893	October 19 - November 17, 2015	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. Enrique Cifuentes, M.D.
Tempe, AZ 85283

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from October 19 to 23, 2015.

After submission of the NDA, OSI received a complaint from an anonymous source about this site's noncompliance with Good Clinical Practice. Examples cited in the complaint included (subjectively) limited documentation of medical history (for example, not reporting surgical history for subjects with evidence of past surgical procedure on chest X-ray and ensuring that subjects with a history of mental illness were not currently taking concomitant medications for treatment of that illness) and study medication administered outside the protocol-specified window.

For Study PT3006, a total of 83 study subjects were screened, and 56 subjects were enrolled and randomized in the study (Note: 10 study subjects were discontinued from the study; four subjects were lost to follow-up, five subjects refused to continue participation, and one subject had adverse event). Forty six study subjects completed the study. An audit of 20 enrolled subjects' records was conducted.

For Study PT3007, a total of 48 study subjects were screened and 30 subjects were enrolled and randomized in the study (Note: 3 study subjects were lost to follow-up). Twenty seven study subjects completed the study. An audit of 10 enrolled subjects' records was conducted.

For extension (rollover from other trials) Study PT3008, a total of 20 study subjects were screened and 20 subjects were enrolled in the study. Twenty study subjects completed the study. An audit of 10 subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. The anonymous complaints were not were not substantiated during this site audit.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

2. V. Jerome Mirkil, M.D.
Las Vegas, NV 89119

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from November 16 to 24, 2015.

After submission of the NDA, OSI received a complaint from an anonymous source about this site's noncompliance with Good Clinical Practice. Examples cited in the complaint included isolated out of window study drug administration times and performance of ECGs for one subject, isolated failure to report adverse event (hypomagnesemia) that subject was being treated for, and failure to add elevated cholesterol noted on laboratory tests to a subject's medical history.

For Study PT3006, a total of 71 study subjects were screened, and 43 subjects were enrolled and randomized in the study (Note: 10 study subjects were discontinued from the study; 9 study subjects refused to continue participation and one subject had an adverse event). Thirty three study subjects completed the study. An audit of 52 of 71 screened subjects' records was conducted.

For Study PT3007, a total of 27 study subjects were screened and 15 subjects were enrolled and randomized in the study (Note: one subject was lost to follow-up). Fourteen study subjects completed the study. An audit of 21 of the 27 screened subjects' records was conducted.

For extension (rollover from other trials) Study PT3008, a total of 69 study subjects were screened, and 16 subjects were enrolled in the study (Note: one subject withdrew consent). Fifteen study subjects completed the study. An audit of 15 subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. The anonymous complaints were not considered to be critical and were not substantiated during this site audit.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

3. **Andrew Garver, Jr. M.D.**
   Andalusia, AL 36420

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

The inspection was conducted from October 5 to 9, 2015.

For Study PT3006, a total of 37 study subjects were screened, and 37 subjects were enrolled, randomized, and completed the study. An audit of 18 enrolled subjects' records was conducted.

Source documents for all enrolled subjects were reviewed and compared to case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted.

There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

The study appears to have been conducted adequately, and the data generated by this site appear acceptable and may be used in support of this specific indication.

Sponsor inspection

4. Pearl Therapeutics, Inc.
Morristown, NJ 07960

The inspection was conducted from October 19 to November 17, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

Following submission of the NDA OSI received a complaint from an anonymous source of continued sponsor noncompliance with the investigational plan and inadequate monitoring.

A Form FDA 483 was issued at the end of the sponsor inspection for failure to ensure proper monitoring of the study and to ensure the study was conducted in accordance with the investigational plan. Additionally, documentation related to financial disclosure of some investigators and complete investigator statements (Form FDA 1572s) were not obtained prior to enrollment of subjects at some sites.

Examples related to inadequate monitoring and documentation deficiencies include

1) The sponsor's monitors did not review the investigator study file as required by the study monitoring plan. Therefore, some documentation, such as required clinical investigator signatures on protocol face sheets were not signed.

2) Regulatory deficiencies were found with sponsor oversight of the clinical trial studies.

   The Data Monitoring Committee did not comply with the charter, in that further meetings were suspended after the November 20, 2014 meeting.

   The DMC charter indicated that the DMC was to hold its last meeting following the database freeze. Following the November 2014 meeting that took place, 47 sites for PT3006, 41 sites for PT-3007, and 56 sites for PT3008 continued to see subjects. The charter-required meeting that was to occur after the database freeze was not convened.

   Additionally, charter was signed by the adjudication committee prior to the initiation of the study.

3) The sponsor did not obtain a complete investigator statement form (Form FDA 1572) before permitting a clinical site investigator to participate in a clinical investigation.

Specifically, the sponsor did not ensure that the clinical investigators listed the imaging facility on this investigator statement form for Study PT3006 and extension Study PT3008 involving 139 of 154 clinical sites and for Study PT3007 and extension Study PT3008 involving 119 out of 140 clinical sites. Additionally, the investigator statement form was not completed prior to the site enrolling the first study subject for the following clinical study sites: 00601, 006102, 006090, 006133, and 006126.

The sponsor responded adequately to the List of Inspectional Observations originally on December 4, 2015 and the sponsor's corrective and preventive action plans were presented and were acceptable.

Notwithstanding the above regulatory deficiencies that were not critical, data submitted by this sponsor appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H., Team Leader, and for
Kassa Ayalew, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Central Doc. Rm.
Review Division /Division Director/Badrul Chowdhury
Review Division /Medical Team Leader/Anthony Durmowicz
Review Division /Project Manager/Brandi Wheeler
Review Division/MO/Anthony Orencia
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

ANTHONY J ORENCIA
03/23/2016

JANICE K POHLMAN
03/23/2016
Signing also for Kassa Ayalew, MD, MPH, Branch Chief

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 11, 2016
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate)
Dosage Form and Route:	inhalation aerosol, for oral inhalation use
Application Type/Number:	NDA 208294
Applicant:	Pearl Therapeutics, Inc.

1 INTRODUCTION

On June 25, 2015, Pearl Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 208294 for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) inhalation aerosol. The proposed indication for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) is for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on July 14, 2015 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) inhalation aerosol.

2 MATERIAL REVIEWED

- Draft BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) MG and IFU received on June 25, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 1, 2016.
- Draft BEVESPI AEROSPHERE (glycopyrrolate and formoterol fumarate) Prescribing Information (PI) received on June 25, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 1, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
03/11/2016

MEETA N PATEL
03/11/2016

LASHAWN M GRIFFITHS
03/11/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: March 9, 2016

To: Brandi Wheeler
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208294
OPDP Comments for BEVESPI AEROSPHERE™ (glycopyrrolate and formoterol fumarate) inhalation aerosol, for oral inhalation use, PI, MG, and IFU

OPDP has reviewed the proposed draft PI, received on March 1, 2016, and have the following comments. Comments on the patient labeling will be submitted under a separate cover as a joint review with DMPP.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
03/09/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 24, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 208294
Product Name and Strength:	Bevespi Aerosphere (Glycopyrrolate and Formoterol Fumarate) Metered Dose Inhaler 9 mcg/4. 8 mcg per inhalation
Product Type:	Drug Device Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pearl Therapeutics, Inc.
Submission Date:	June 25, 2015
OSE RCM #:	2015-1581
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

As part of the evaluation for NDA 208294 submitted on June 25, 2015, DPARP requested DMEPA evaluate the proposed container labels, carton labeling, medication guide and Full Prescribing Information (FPI) for Bevespi Aerosphere for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This is a combination product containing glycopyrrolate and formoterol fumarate. Both glycopyrrolate and formoterol fumarate are currently marketed as single ingredient products or in combination with other ingredients in different dosage forms.

We performed a risk assessment of the proposed container labels, carton labeling, medication guide and full prescribing information to identify deficiencies that may lead to medication errors.

DMEPA finds that the label and labeling can be improved to promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Pearl Therapeutics, Inc. increase the readability and prominence of important information in the proposed labeling to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR PEARL THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. All Label and Labeling

1. Revise the presentation of the strength and dosage form so that it is easily recognized:

   Bevespi Aerosphere
   (Glycopyrrolate and Formoterol Fumarate) Inhalation Aerosol
   9 mcg/4.8 mcg per inhalation

2. Ensure that the modifier 'Aerosphere' has equal prominence to the root name 'Bevespi'.

B. Carton Labeling

1. Relocate 'Shake inhaler well before using' from the side panel to the principal display panel to mitigate the risk that this important information this overlooked. To allow space for this statement, we recommend you consider decreasing the size of the graphics.
2. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual carton as required per 21CFR 201.25(c)(2).
3. Remove the statement (b) (4)
4. For consistency with the full Prescribing Information, revise the 'Discard the inhaler…' statement under 'Date foil pouch opened:' to read: Discard the inhaler when the labeled number of inhalations have been used or within 3 months of opening the foil pouch, *whichever comes first.*'

C. Canister Label

1. Add the lot and expiration date to the canister label.

D. Carton Labeling and Overwrap Foil

1. Revise the usual dosage statement to read: '2 inhalations twice daily'.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bevespi Aerosphere that Pearl Therapeutics Inc. submitted on June 25, 2015.

Table 2. Relevant Product Information for Bevespi Aerosphere	
Initial Approval Date	N/A
Active Ingredient	Glycopyrrolate and Formoterol Fumarate
Indication	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Route of Administration	Oral inhalation
Dosage Form	Metered Dose Inhaler (MDI)
Strength	9 mcg/4.8 mcg per inhalation
Dose and Frequency	2 inhalations twice daily
How Supplied	Pressurized aluminum canister with an attached dose indicator, a white plastic actuator and mouthpiece, and an orange dust cap
Storage	Controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP].

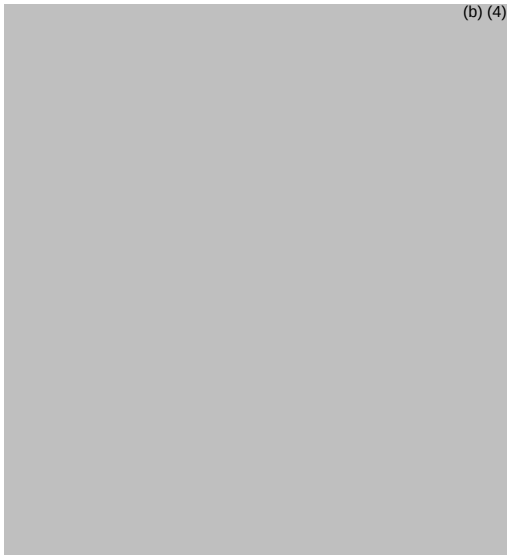
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Bevespi Aerosphere labels and labeling submitted by Pearl Therapeutics Inc. on June 25, 2015.

- Container label
- Carton labeling
- Instructions for Use (no image)
- Full Prescribing Information (no image)
- Medication Guide (no image)

G.2 Label and Labeling Images



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Canister

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C OWENS
02/24/2016

MISHALE P MISTRY
02/24/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 208294
Brand Name	BEVESPI AEROSPHERE
Generic Name	Glycopyrronium/Formoterol
Sponsor	Pearl Therapeutics
Indication	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Dosage Form	Inhaler
Drug Class	β2-agonist (formoterol fumarate) and anticholinergic (glycopyrrolate)
Therapeutic Dosing Regimen	Glycopyrronium 18 µg/Formoterol fumarate 9.6 µg administered twice daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not identified
Submission Number and Date	SDN 001/New NDA; 25 Jun 2015
Review Division	DPARP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of glycopyrronium/formoterol (GFF MDI 14.4/9.6 µg and GFF MDI 115.2/38.4 µg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between glycopyrronium/formoterol (GFF MDI 14.4/9.6 µg and GFF MDI 115.2/38.4 µg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, blinded, five-period crossover study, 69 healthy subjects received GFF MDI 14.4/9.6 µg, GFF MDI 115.2/38.4 µg, GP MDI 115.2 µg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Glycopyrronium/Formoterol (GFF MDI 14.4/9.6 µg and GFF MDI 115.2/38.4 µg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
GFF MDI 14.4/9.6 µg	0.17	3.2	(1.3, 5.0)
GFF MDI 115.2/38.4 µg	0.33	7.6	(5.7, 9.5)
GP MDI 115.2 µg	12	0.7	(-1.2, 2.6)
Moxifloxacin 400 mg*	2	9.3	(6.9, 11.7)

* Multiple endpoint adjustment of 3 time points was applied.

For glycopyrronium, the supratherapeutic dose of GFF (115.2/38.4 µg) produced a mean Cmax value of 60 pg/mL that is 4.9-fold the Cmax at the single therapeutic dose of GFF (14.4/9.6 µg) and 3.5-fold the steady state Cmax with the proposed therapeutic dose.

For formoterol, 115.2/38.4 µg-dose produced a mean Cmax that is 3.4 -fold the Cmax at the the single therapeutic dose of GFF (14.4/9.6 µg) and 2.6-fold the steady state Cmax with the proposed therapeutic dose. Hepatic impairment may decrease formoterol fumarate clearance as it is primarily eliminated via hepatic metabolism. However, exposure data in patients with hepatic or renal impairment are not available. A significant relationship between formoterol fumarate concentrations and ΔΔQTcI was observed. Therefore, a marginal QT prolongation might be expected at the GFF dose of 14.4/9.6 µg in some hepatic impairment patients.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Glycopyrronium's QT effect was also evaluated in NDA 207923 and NDA 207930. No significant QT prolongation effect glycopyrrolate at the supratherapeutic dose of 400 µg (with mean Cmax of 1495 pg/mL) was detected in the TQT study. No evident relationship between glycopyrrolate plasma concentration and ΔΔQTcF was observed.

- A significant relationship between formoterol fumarate concentrations and ΔΔQTcI was observed. The supratherapeutic dose of GFF (115.2/38.4 µg) produced a 2.6-fold margin compared to the therapeutic exposure. Exposure data in patients with hepatic or renal impairment are not available. However, since formoterol fumarate is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of formoterol fumarate in plasma. Therefore, a marginal QT prolongation might be expected at the GFF dose of 14.4/9.6 µg in some hepatic impairment patients.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiovascular effects: *Healthy Subjects*
The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. (b) (4)

A dose-dependent increase in heart rate was also observed. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected heart rate were 3.3 (4.9) beats/min and 7.6 (9.5) beats/min seen within 10 minutes of dosing with 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, respectively. (b) (4)

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiovascular effects: *Healthy Subjects*
The potential for QTc interval prolongation was assessed in a double-blind, single-dose, placebo- and positive-controlled crossover trial in 69 healthy subjects. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected QTcI for 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. (b) (4)

A dose-dependent increase in heart rate was also observed. The largest mean (90% upper confidence bound) differences from placebo in baseline-corrected heart rate were 3.3 (4.9) beats/min and 7.6 (9.5) beats/min seen within 10 minutes of dosing with 2 inhalations of BEVESPI AEROSPHERE and glycopyrrolate/formoterol fumarate 72/19.2 mcg, respectively (b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Glycopyrronium and Formoterol Fumarate (GFF) Inhalation Aerosol (henceforth referred to as Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler [MDI], GFF MDI, or PT003), is a fixed-dose combination of glycopyrrolate (glycopyrronium bromide) 9 μg and formoterol fumarate 4.8 μg to be administered via oral inhalation. Glycopyrronium is a long acting muscarinic antagonist (LAMA), and formoterol fumarate is a selective long-acting β2 antagonist (LABA). GFF MDI is indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema at the recommended dose of two inhalations (i.e. 18 μg of glycopyrrolate [glycopyrronium bromide], equivalent to 14.4 μg of glycopyrronium, and 9.6 μg of formoterol fumarate) twice daily (BID).

3.2 MARKET APPROVAL STATUS

GFF is not approved for marketing in any country. Cuvposa (glycopyrrolate) Oral Solution was approved by FDA on 6/28/2010 to treat chronic severe drooling caused by neurologic disorders. Foradil Aerolizer (formoterol fumarate inhalation powder) was approved by FDA in Feb. 2001.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

Formoterol fumarate is associated with increased heart rate (HR), maximum rate of rise of left ventricular pressure (dp/dt), pulmonary artery and capillary pressure, coronary blood flow, cardiac output and myocardial oxygen consumption. Decreased peripheral pulmonary and coronary resistances were also observed.

3.4 PREVIOUS CLINICAL EXPERIENCE

Refer QT-IRT consult review (05/03/2012).

Also see Appendix 6.1.

In approved Foradil label, the following QT related languages were included:

5.6 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs [*see Overdosage (10)*].

Formoterol fumarate, like other beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of FORADIL AEROLIZER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, formoterol fumarate, like other sympathomimetic amines, should

be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

12.2 Pharmacodynamics

Systemic Safety and Pharmacokinetic/Pharmacodynamic Relationships

The major adverse effects of inhaled beta$_2$-agonists occur as a result of excessive activation of the systemic betaadrenergic receptors. The most common adverse effects in adults and adolescents include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between heart rate, ECG parameters, and serum potassium levels and the urinary excretion of formoterol were evaluated in 10 healthy male volunteers (25 to 45 years of age) following inhalation of single doses containing 12, 24, 48, or 96 mcg of formoterol fumarate. There was a linear relationship between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate.

In a second study, PK/PD relationships between plasma formoterol levels and pulse rate, ECG parameters, and plasma potassium levels were evaluated in 12 healthy volunteers following inhalation of a single 120 mcg dose of formoterol fumarate (10 times the recommended clinical dose). Reductions of plasma potassium concentration were observed in all subjects. Maximum reductions from baseline ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. The formoterol plasma concentration was highly correlated with the reduction in plasma potassium concentration. Generally, the maximum effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved. A mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose. The maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12-24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on plasma potassium, pulse rate, and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at the very high formoterol dose (120 mcg single dose, 10 times the recommended single dose) tested in this study. These effects were well-tolerated by the healthy volunteers.

The electrocardiographic and cardiovascular effects of FORADIL AEROLIZER were compared with those of albuterol and placebo in two pivotal 12-week double-blind studies of patients with asthma. A subset of patients underwent continuous electrocardiographic monitoring during three 24-hour periods. No important differences in ventricular or supraventricular ectopy between treatment groups were observed. In these two studies, the total number of patients with asthma exposed to any dose of FORADIL AEROLIZER who had continuous electrocardiographic monitoring was about 200.

Continuous electrocardiographic monitoring was performed in an 8-week, randomized, double-blind, and placebo controlled trial in 204 COPD patients treated with FORADIL AEROLIZER 12 mcg twice daily or placebo. Holter monitoring was used to evaluate predefined proarrhythmic events. Non-sustained ventricular tachycardia occurred in 2 (2.2%) of FORADIL AEROLIZER treated patients compared to none in the placebo group. An increase in ventricular premature beats (VPB) occurred in 3 (3.3 %) of FORADIL AEROLIZER treated patients compared to 2 (1.9%) in the placebo group. There were no events of sustained ventricular tachycardia, ventricular flutter or fibrillation, or symptomatic runs of VPB. One patient in the FORADIL AEROLIZER group had a serious adverse event of atrial flutter.

The electrocardiographic effects of FORADIL AEROLIZER were evaluated versus placebo in a 12-month pivotal double-blind study of patients with COPD. An analysis of ECG intervals was performed for patients who participated at study sites in the United States, including 46 patients treated with FORADIL AEROLIZER 12 mcg twice daily, and 50 patients treated with FORADIL AEROLIZER 24 mcg twice daily. ECGs were performed predose, and at 5-15 minutes and 2 hours post-dose at study baseline and after 3, 6 and 12 months of treatment. The results showed that there was no clinically meaningful acute or chronic effect on ECG intervals, including QTc, resulting from treatment with FORADIL AEROLIZER.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of GFF's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 107739. The sponsor submitted the study report PT003009 for glycopyrronium/formoterol, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, double-blind, single-dose, five-treatment, cross-over study to assess the cardiovascular safety (including QT/QTc intervals) of two dose levels (one therapeutic and one supra-therapeutic) of glycopyrronium and formoterol fumarate metered dose inhaler (GFF MDI) and a supra-therapeutic dose of glycopyrronium metered dose inhaler (GP MDI) in healthy adult volunteers, compared with moxifloxacin (400 mg open-label) as the positive control

4.2.2 Protocol Number

PT003009

4.2.3 Study Dates

24 Nov 2013 -- 19 Dec 2013

4.2.4 Objectives

Primary objectives:
Safety: To evaluate the effect of a single orally inhaled dose of GFF MDI at two doses and a single orally inhaled dose of GP MDI at a supra-therapeutic dose on the heart rate corrected QT interval (QTc).
Efficacy: This was a cardiac safety study in healthy volunteers; study drug efficacy was not evaluated.

Secondary objectives:

- To establish assay sensitivity by demonstrating the effect of a single oral dose of 400 mg moxifloxacin on QTc.

- To evaluate the effect of a single orally inhaled dose of GFF MDI at two doses(one therapeutic and one supra-therapeutic) and a single orally inhaled dose of GP MDI at a supra-therapeutic dose on heart rate, PR and QRS intervals including outlier analysis and T wave morphology changes.
- To evaluate the safety and tolerability of a single orally inhaled dose of GFF MDI at two doses and a single orally inhaled dose of GP MDI at a supra-therapeutic dose.
- To determine the PK of a single orally inhaled dose of GFF MDI at two doses and the PK of a single orally inhaled dose of GP MDI at a supra-therapeutic dose.
- To determine the relationship between QT/QTc and plasma concentration of glycopyrronium and formoterol following administration of GFF MDI and the relationship between QT/QTc and plasma concentration of glycopyrronium following administration of GP MDI.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 10-sequence, crossover design with five dosing occasions. Each dosing occasion was followed by a washout period of at least five days.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded, whereas the other treatments were double-blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 5 treatments:

- GFF MDI 14.4/9.6 µg
- GFF MDI 115.2/38.4 µg
- GP MDI 115.2 µg
- Placebo MDI
- Moxifloxacin 400 mg

GFF MDI and GP MDI were designed to be delivered by oral inhalation. The placebo was designed to be delivered by oral inhalation using a MDI. Moxifloxacin 400 mg (one tablet) was administrated orally.

4.2.6.2 Sponsor's Justification for Doses

The thorough QT/QTc study used supratherapeutic doses of 115.2/38.4 µg GFF MDI (i.e., 115.2 µg glycopyrronium, equivalent to 144 µg glycopyrrolate, and 38.4 µg formoterol) and 115.2 µg GP MDI (i.e., 115.2 µg glycopyrronium, equivalent to 144 µg

glycopyrrolate) in healthy volunteers in order to account for potential accumulation at steady state. Coverage for approximately 2-fold accumulation with formoterol and 4-fold accumulation with glycopyrronium was included based on earlier PK studies.

The doses of glycopyrronium in GFF MDI used in the pharmacokinetic studies were typically higher than the recommended GFF MDI dose of 18/9.6 µg single dose or 36/19.2 µg total daily dose (i.e., 18 µg glycopyrrolate and 9.6 µg formoterol single dose or 36 µg glycopyrrolate and 19.2 µg formoterol total daily dose, equivalent to 14.4 µg glycopyrronium and 9.6 µg formoterol single dose or 36 µg glycopyrronium and 19.2 µg formoterol total daily dose, respectively). The doses of formoterol used in the Glycopyrronium and Formoterol Fumarate Inhalation Aerosol Pearl Therapeutics pharmacokinetic studies were typically within the range of the recommended dose for approved drugs containing formoterol.

Reviewer's Comment:

The doses selected by the sponsor in this study are appropriate. for glycopyrronium, the supratherapeutic dose (115.2/38.4 µg) produces mean Cmax values 4.9-fold the Cmax at the single therapeutic dose (14.4/9.6 µg) and 3.5-fold the steady state Cmax at the multiple therapeutic dose.

For formoterol, 115.2/38.4 µg-dose produced a mean Cmax that is 3.4 -fold the Cmax at the the single therapeutic dose of GFF (14.4/9.6 µg) and 2.6-fold the steady state Cmax with the proposed therapeutic dose. Hepatic impairment may decrease formoterol fumarate clearance as it is primarily eliminated via hepatic metabolism. However, exposure data in patients with hepatic or renal impairment are not available. A significant relationship between formoterol fumarate concentrations and ΔΔQTcI was observed. Ultimately, the adequacy of the doses will be determined once the effects of all relevant intrinsic and extrinsic factors on the PK of formoterol are known.

4.2.6.3 Instructions with Regard to Meals

Subjects fasted for at least eight hours prior to dosing and for four hours post-dosing in each period. For clinical laboratory assessment blood draws, subjects fasted for at least four hours. Meals during the dosing day of each period were standardized.
The 400 mg moxifloxacin tablet was administered with 250 mL of water. Otherwise, there were no restrictions regarding fluid intake.
Reviewer's Comment: GFF MDI is administered by oral inhalation and the drug absorption is not likely to be influenced by food.

4.2.6.4 ECG and PK Assessments

ECG assessments:
ECG was extracted from continuous 24-hour Holter recordings at predose (-0.75, -0.5 and -0.25 hour), and 2, 6, 10, 20, and 40 minutes and 1, 2, 3, 5, 8, 12, and 24 hours post-dose. During protocol-specified ECG extraction windows, 10 replicates of 14 second digital 12-lead ECG tracings, each recorded after at least a three minute supine rest period were obtained.

PK assessments:

Blood samples for the determination of plasma concentrations of glycopyrronium and formoterol in plasma were collected predose (-1 hour), and at 2, 6, 10, 20, and 40 minutes and 1, 2, 3, 5, 8, 12, and 24 hours post-dose.

Reviewer's Comment: The sponsor's PK and ECG sampling is appropriate for identifying peak glycopyrronium and formoterol *concentrations, and is sufficient to characterize the time-course.*

4.2.6.5 Baseline

The average of predose QT/QTc values on dose administration day of each period was used as baseline for that period.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 70 healthy subjects were randomized to the study. Sixty nine subjects received at least one of the five study drugs and all of them were included in the safety analysis set and the PK analysis set. Sixty subjects completed the study.

For the 69 subjects who received treatment with at least one of the five study drugs, the mean age was 31.0 ±8.0 years (median: 28.0 years) and ranged from 19 to 45 years. Overall, 44 (63.8%) subjects were male and 25 (36.2%) were female.

Fifty-five (79.7%) of the subjects were Black/African American, 11 (15.9%) were White and 3 (4.3%) subjects were documented as "other". Eight (11.6%) subjects were Hispanic or Latino, while the remaining 61 (88.4%) subjects were of some other ethnic origin.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The largest LS mean placebo-corrected ΔQTcI (ΔΔQTcI) value following single dose treatment with GFF MDI 115.2/38.4 µg was observed 20 minutes post-dosing and was 7.6 msec with an upper bound of the 90% CI of 9.2 msec. The largest LS mean ΔΔQTcI following single dose administration with GFF MDI 14.4/9.6 µg was observed at approximately 10 minutes post-dosing and was 3.1 msec with an upper bound of the 90% CI value of 4.7 msec. The 90% CI's for ΔΔQTcI for both GFF MDI 14.4/9.6 µg and GP MDI 115.2 µg were below 5 msec at all time points, which is considerably less than the non-inferiority margin of 10 msec. Therefore, it can be concluded that there is no clinically meaningful effect on QT following single dose administration with these treatments.

The sponsor's results for primary analysis are displayed in the following Table 2 and Table 3.

Table 2: Statistical Comparisons of QTcI Change from Baseline over Time by Treatment Group (Sponsor's Results Based on Safety Population)

Treatment/Time Point (hours)	Change from Baseline (msec)		Estimated Difference from Placebo (msec)	
	LS Mean (±SE)	90% CI Lower, Upper	LS Mean (±SE)	90% CI Lower, Upper
GFF MDI 14.4/9.6 µg				
0.03	-3.6 (0.7)	-4.8, -2.4	0.9 (0.9)	-0.6, 2.5
0.1	1.8 (0.7)	0.6, 3.0	2.5 (0.9)	1.0, 4.0
0.17	1.7 (0.8)	0.4, 3.0	3.1 (1.0)	1.4, 4.7
0.33	0.5 (0.7)	-0.7, 1.7	1.5 (0.9)	0.0, 3.1
0.67	-0.3 (0.8)	-1.6, 1.1	1.1 (1.1)	-0.7, 2.8
1	-0.8 (0.8)	-2.2, 0.5	1.7 (1.1)	0.0, 3.5
2	-1.9 (0.8)	-3.1,-0.6	2.4 (1.0)	0.8, 4.0
3	-1.9 (0.8)	-3.2, -0.5	1.2 (1.0)	-0.5, 3.0
5	-0.4 (1.2)	-2.5, 1.6	1.3 (1.7)	-1.5, 4.1
8	-5.4 (1.1)	-7.2,-3.7	1.2 (1.4)	-1.2, 3.5
12	-3.9 (1.0)	-5.5, -2.4	2.2 (1.3)	0.1, 4.3
24	-5.7 (1.0)	-7.3, -4.1	0.6 (1.3)	-1.5, 2.7
GFF MDI 115.2/38.4 µg				
0.03	-2.5 (0.8)	-3.8, -1.3	2.0 (0.9)	0.5, 3.6
0.1	4.9 (0.7)	3.7, 6.1	5.7 (0.9)	4.1, 7.2
0.17	5.9 (0.8)	4.6, 7.3	7.3 (1.0)	5.6, 9.0
0.33	6.6 (0.8)	5.3, 7.9	7.6 (1.0)	6.0, 9.2
0.67	5.4 (0.8)	4.0, 6.8	6.8 (1.1)	5.0, 8.5
1	4.0 (0.8)	2.7, 5.4	6.6 (1.1)	4.9, 8.4
2	3.0 (0.8)	1.7, 4.3	7.3 (1.0)	5.6, 8.9
3	3.6 (0.8)	2.3, 5.0	6.7 (1.0)	5.0, 8.4
5	3.0 (1.3)	0.9, 5.1	4.8 (1.7)	2.0, 7.6

Table 3: Statistical Comparisons of QTcI Change from Baseline over Time by Treatment Group (Sponsor's Results Based on Safety Population Continue)

Treatment/Time Point (hours)	Change from Baseline (msec)		Estimated Difference from Placebo (msec)	
	LS Mean (±SE)	90% CI Lower, Upper	LS Mean (±SE)	90% CI Lower, Upper
8	-2.8 (1.1)	-4.6, -1.1	3.7 (1.4)	1.4, 6.1
12	-2.1 (1.0)	-3.8, -0.5	4.0 (1.3)	1.9, 6.2
24	-6.4 (1.0)	-8.0, -4.7	-0.1 (1.3)	-2.2, 2.1
GP MDI 115.2 µg				
0.03	-5.0 (0.7)	-6.2, -3.7	-0.4 (0.9)	-2.0, 1.2
0.1	-1.0 (0.7)	-2.2, 0.2	-0.3 (0.9)	-1.8, 1.2
0.17	-1.5 (0.8)	-2.8, -0.2	-0.2 (1.0)	-1.8, 1.5
0.33	-1.7 (0.8)	-2.9, -0.4	-0.6 (1.0)	-2.2, 0.9
0.67	-2.3(0.8)	-3.7, -1.0	-1.0 (1.1)	-2.7, 0.8
1	-3.0(0.8)	-4.4, -1.7	-0.4 (1.1)	-2.2, 1.3
2	-4.2 (0.8)	-5.4, -2.9	0.1 (1.0)	-1.5, 1.7
3	-3.5 (0.8)	-4.8, -2.2	-0.4 (1.0)	-2.1, 1.3
5	-3.3 (1.2)	-5.4, -1.3	-1.6 (1.7)	-4.4, 1.2
8	-7.8 (1.1)	-9.5, -6.1	-1.2 (1.4)	-3.5, 1.1
12	-5.3 (1.0)	-6.9, -3.7	0.8 (1.3)	-1.3, 3.0
24	-7.3 (1.0)	-8.9, -5.7	-1.0 (1.3)	-3.1, 1.2
Moxifloxacin 400 mg				
0.03	-3.2 (0.7)	-4.5, -2.0	1.3 (0.9)	-0.2, 2.9
0.1	0.2 (0.7)	-1.0, 1.4	0.9 (0.9)	-0.5, 2.4
0.17	-0.5 (0.8)	-1.8, 0.8	0.8 (1.0)	-0.8, 2.5
0.33	-0.6 (0.7)	-1.9, 0.6	0.4 (0.9)	-1.2, 2.0
0.67	4.9 (0.8)	3.6, 6.3	6.3 (1.1)	4.5, 8.0
1	5.8 (0.8)	4.4, 7.1	8.3 (1.1)	6.6, 10.1
2	5.0 (0.8)	3.7, 6.3	9.3 (1.0)	7.7, 10.9
3	5.6 (0.8)	4.3, 6.9	8.7 (1.0)	7.0, 10.4
5	3.1 (1.2)	1.1, 5.1	4.8 (1.7)	2.0, 7.6
8	-0.6 (1.0)	-2.4, 1.1	5.9 (1.4)	3.6, 8.3
12	-0.2 (1.0)	-1.7, 1.4	6.0 (1.3)	3.9, 8.1
24	-3.5 (1.0)	-5.1, -1.9	2.8 (1.3)	0.7, 4.9

Source: clinical study report PT003009,Table 13, page 62

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

Assay sensitivity was confirmed by the QTcI effect that was observed during treatment with moxifloxacin (positive control) with a peak mean ΔΔQTcI of 9.3 msec 2 hours after dosing with the lower bound of the 90% CI above 6 msec at all pre-specified time points (1, 2, and 3 hours post-dosing).

The sponsor's results for assay sensitivity analysis are displayed in the above Table 3.

Reviewer's Comments: please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

In terms of the incidence of subjects having absolute category QTcI outlier values, there were no subjects with either a >480 msec or >500 msec outlier value. However, 1 (2%) subject after treatment with GFF MDI 14.4/9.6 µg, 3 (5%) subjects for GFF MDI 115.2/38.4 µg, 1 (2%) subject for GP 115.2 µg, and 1 (2%) subject for moxifloxacin had one or more >450 msec QTcI outlier. No placebo-treated subject had a QTcI outlier in any of the three categories.

In terms of the incidence of subjects having a ΔQTcI outlier value, there were no subjects with either a ΔQTcI that was >60 ms or a ΔQTcI value <60 ms along with a QTcI value ≤500 ms. However, 2 (3%) subjects after treatment with GFF MDI 115.2/38.4 µg, 2 (3%) subjects for GP 115.2 µg, 2 (3%) subjects for moxifloxacin and 1 (2%) subject for placebo had one or more ΔQTcI that was >30 ms. No subject after treatment with GFF MDI 14.4/9.6 µg had a ΔQTcI in any of the three categories.

4.2.8.3 Safety Analysis

No subject after receiving any treatment experienced an SAE and there were no subject deaths for any treatment during the study.

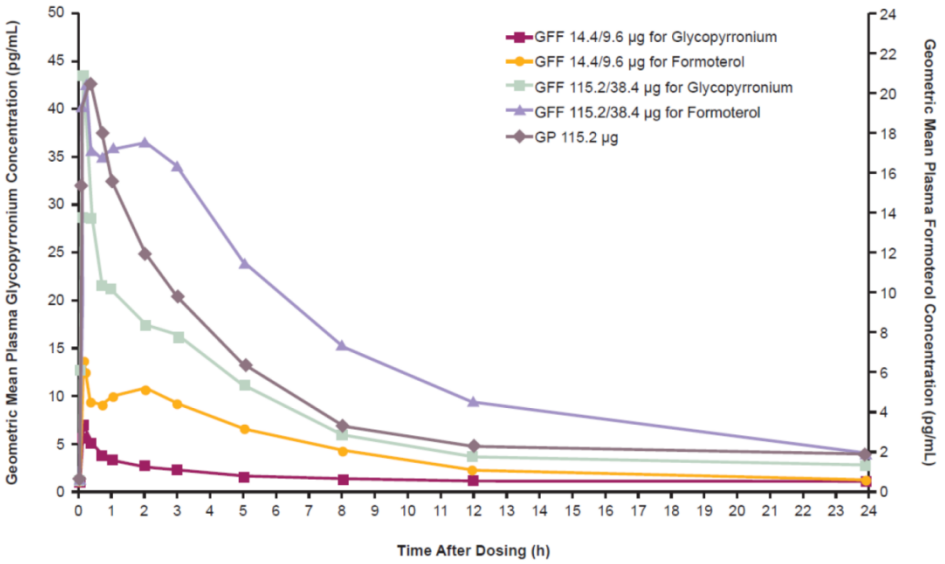
A total of 3 (4.3%) subjects were discontinued due to a TEAE. One subject was discontinued due to atrial fibrillation after receiving GP MDI 115.2 µg, another subject after receiving GFF MDI 14.4/9.6 µg was discontinued due to ECG PR prolongation and a third subject after receiving GFF MDI 115.2/38.4 µg was discontinued due to tremor.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

For glycopyrronium, the supratherapeutic dose of GFF (115.2/38.4 µg) produces mean Cmax values 4.9-fold the Cmax at the single therapeutic dose (14.4/9.6 µg) and 3.5-fold the steady state Cmax at multiple therapeutic dose. For formoterol, 115.2/38.4 µg GFF dose produces Cmax 3.4-fold the Cmax at the single 14.4/9.6 µg dose and 2.6-fold the steady state Cmax at the multiple 14.4/9.6 µg dose.

Figure 1: **Geometric Mean Plasma Concentration-Time Profile (Linear Scale) of Glycopyrronium and Formoterol (Safety Population)**



Source: clinical study report PT003009,Figure 13, page 94

Table 4: GFF MDI Pharmacokinetic Parameters

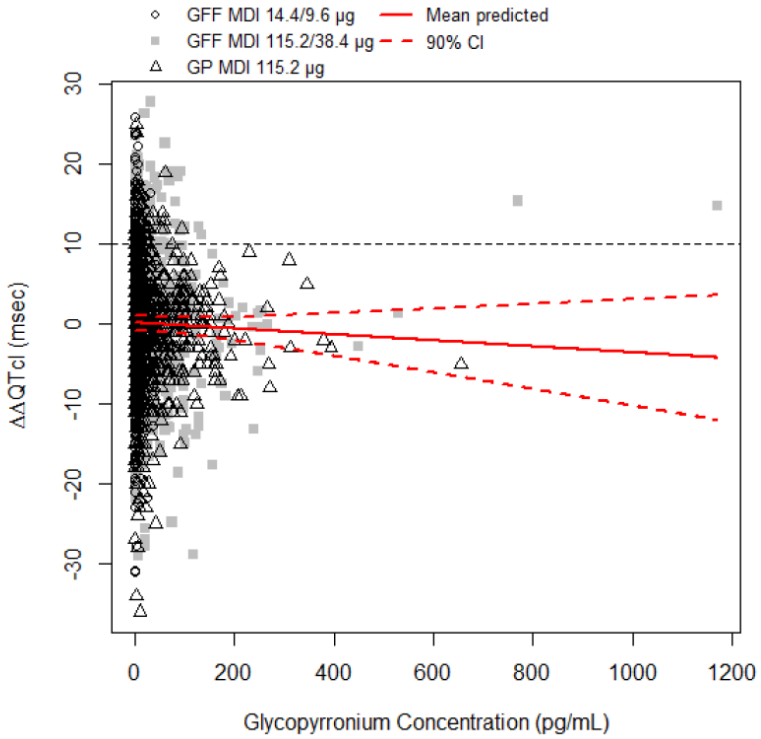
PK Parameter	Glycopyrronium PK Parameters			Formoterol PK Parameters	
	GFF MDI 14.4/9.6 µg (N=66)	GFF MDI 115.2/38.4 µg (N=66)	GP MDI 115.2 µg (N=66)	GFF MDI 14.4/9.6 µg (N=66)	GFF MDI 115.2/38.4 µg (N=66)
AUC_{0-12} (h*pg/mL)	20.79 (122.0)	152.26 (65.0)	183.19 (74.3)	36.29 (55.5)	135.69 (45.2)
AUC_{0-t} (h*pg/mL)	18.61 (151.6)	177.34 (81.6)	226.31 (88.0)	36.39 (72.5)	169.28 (50.0)
AUC_{0-inf} (h*pg/mL)	29.05 (59.2)	233.11 (91.5)	381.78 (87.0)	55.45 (46.0)	205.98 (49.0)
AUC_{extr} (%)	33.72 (31.8)	18.55 (55.9)	22.86 (56.5)	21.86 (39.8)	13.03 (43.9)
C_{max} (pg/mL)	12.26 (85.4)	60.30 (147.5)	64.05 (122.5)	9.68 (71.1)	33.63 (65.2)
T_{max} (hours)	0.10	0.10	0.17	0.17	0.17
λ-z (1/hours)	0.25 (57.4)	0.09 (97.3)	0.06 (92.4)	0.12 (48.9)	0.09 (32.5)
t½ (hours)	2.81 (57.4)	7.73 (97.3)	12.26 (92.4)	5.84 (48.9)	8.17 (32.5)
CL/F (L/hour)	495.73 (59.2)	494.18 (91.5)	301.74 (87.0)	173.14 (46.0)	186.43 (49.0)
Vd/F (L)	2012.41 (30.0)	5509.81 (59.0)	5336.95 (59.6)	1459.82 (38.0)	2196.21 (46.9)

Source: clinical study report PT003009,Table 25, page 95

4.2.8.4.2 Exposure-Response Analysis

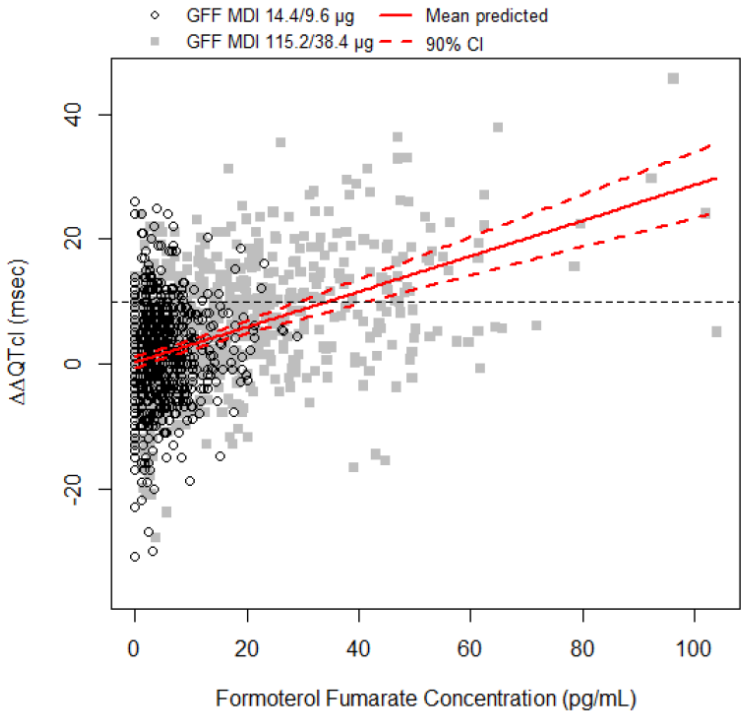
A statistically significant relationship between ΔΔQTcI and formoterol plasma concentrations was demonstrated with a slope of 0.285 ms per pg/mL (90% CI: 0.227; 0.343 pg/mL). The slope for the relationship to glycopyrronium plasma concentrations was shallow and not significant (p=0.3636) (Figure 2). Using this model, a ΔΔQTcI effect of around 9.6 ms (upper bound of 90% CI: 11.2 ms) can be projected at the observed geometric mean formoterol plasma concentration (32.9 pg/mL) after a supra-therapeutic dose of 38.4 µg FF. This projected effect is somewhat larger than the observed mean peak ΔΔQTcI effect in the analysis by time point after dosing with GFF MDI 115/38.4 µg. A concentration-dependent, statistically significant, slightly negative relationship was however also noted for the FF-GP interaction, which may indicate co-administration somewhat reduces the ΔΔQTcI effect. The observed data for FF with population mean predictions are provided in Figure 3 for subjects who received either the therapeutic or supra-therapeutic dose of GFF MDI.

Figure 2: Observed Data for GP with Population Mean Predictions (Solid Red Line)



Source: clinical study report PT003009,Figure 15, page 99

Figure 3: Observed Data for FF with Population Mean Predictions (Solid Red Line)



Source: clinical study report PT003009,Figure 14, page 98

Reviewer's Analysis: We will provide our independent analysis results in Section 5.2. Our analyses results are similar to those provided by the sponsor.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

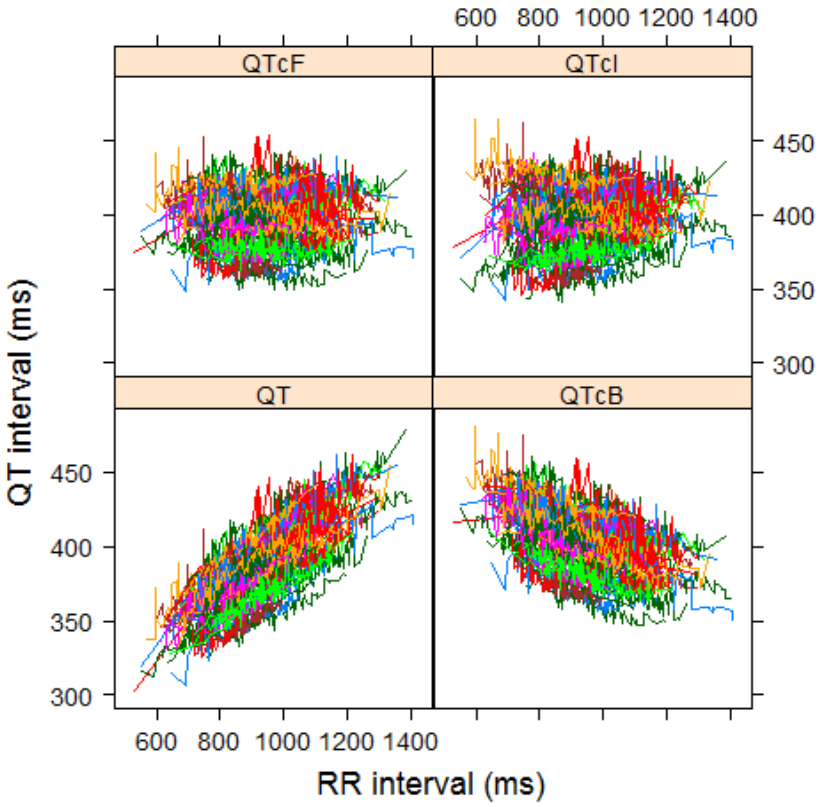
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it appears that QTcF and QTcI correct QT almost equally well. Therefore, this statistical reviewer used QTcI for the primary statistical analysis.

Table 5: Average of Sum of Squared Slopes for Different QT-RR CorrectionMethods

	QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**
Placebo MDI	63	0.00144	63	0.00182
Moxifloxacin 400 mg	67	0.00219	67	0.00199
GFF MDI 14.4/9.6 µg	66	0.00233	66	0.00235
GFF MDI 115.2/38.4 µg	64	0.00300	64	0.00398
GP MDI 115.2 µg	65	0.00138	65	0.00143
All	69	0.00090	69	0.00091

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Glycopyrronium/Formoterol

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model includes treatment, time point, sequence, period, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 6: Analysis Results of ΔQTcI and ΔΔQTcI for Treatment Group = GFF MDI 14.4/9.6 µg

	ΔQTcI (ms) GFF MDI 14.4/ 9.6 µg	ΔQTcI (ms) Placebo	ΔΔQTcI (ms) GFF MDI 14.4/ 9.6 µg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.03	-3.5	-4.4	1.0	(-0.8, 2.9)
0.1	2.0	-0.5	2.5	(0.7, 4.4)
0.17	1.9	-1.2	3.2	(1.3, 5.0)
0.33	0.7	-0.9	1.6	(-0.3, 3.4)
0.67	-0.1	-1.2	1.2	(-0.7, 3.0)
1	-0.6	-2.4	1.8	(-0.0, 3.7)
2	-1.6	-4.1	2.5	(0.6, 4.3)
3	-1.7	-2.9	1.4	(-0.5, 3.3)
5	-0.2	-1.5	1.5	(-0.4, 3.4)
8	-5.3	-6.5	1.3	(-0.6, 3.2)
12	-3.8	-6.0	2.3	(0.4, 4.1)
24	-5.6	-6.0	0.6	(-1.2, 2.5)

Table 7: Analysis Results of ΔQTcI and ΔΔQTcI for Treatment Group = GFF MDI 115.2/38.4 µg

	ΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	ΔQTcI (ms) Placebo	ΔΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.03	-2.6	-4.4	2.1	(0.2, 4.0)
0.1	4.9	-0.5	5.7	(3.8, 7.6)
0.17	5.9	-1.2	7.4	(5.5, 9.3)
0.33	6.3	-0.9	7.6	(5.7, 9.5)
0.67	5.4	-1.2	6.9	(5.0, 8.8)
1	4.0	-2.4	6.8	(4.9, 8.7)
2	3.0	-4.1	7.3	(5.4, 9.2)
3	3.5	-2.9	6.8	(4.9, 8.7)

	ΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	ΔQTcI (ms) Placebo	ΔΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
5	2.7	-1.5	4.8	(2.9, 6.7)
8	-2.8	-6.5	4.0	(2.1, 5.9)
12	-2.1	-6.0	4.1	(2.2, 6.0)
24	-6.3	-6.0	-0.1	(-2.0, 1.8)

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for Treatment Group = GP MDI 115.2 µg

	ΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	ΔQTcI (ms) Placebo	ΔΔQTcI (ms) GFF MDI 115.2/ 38.4 µg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.03	-5.0	-4.4	-0.5	(-2.4, 1.4)
0.1	-1.1	-0.5	-0.4	(-2.3, 1.5)
0.17	-1.5	-1.2	-0.2	(-2.1, 1.6)
0.33	-1.8	-0.9	-0.8	(-2.7, 1.1)
0.67	-2.4	-1.2	-1.1	(-3.0, 0.8)
1	-3.0	-2.4	-0.5	(-2.4, 1.4)
2	-4.2	-4.1	-0.0	(-1.9, 1.9)
3	-3.6	-2.9	-0.6	(-2.4, 1.3)
5	-3.3	-1.5	-1.7	(-3.6, 0.2)
8	-7.8	-6.5	-1.3	(-3.1, 0.6)
12	-5.4	-6.0	0.7	(-1.2, 2.6)
24	-7.6	-6.0	-1.3	(-3.2, 0.6)

The largest upper bounds of the 2-sided 90% CI for the mean differences between GFFMDI 14.4/9.6 µg and placebo, and between GFF MDI 115.2/38.4 µg and placebo were 5.0 ms and 9.5 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 7.4 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 6.9 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of ΔQTcI and ΔΔQTcI for Moxifloxacin

	ΔQTcI (ms) Moxifloxacin 400 mg	**ΔQTcI (ms) Placebo**	**ΔΔQTcI (ms) Moxifloxacin 400 mg**		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
0.03	-3.2	-4.4	1.3	(-0.6, 3.2)	(-1.1, 3.8)
0.1	0.0	-0.5	0.7	(-1.1, 2.6)	(-1.7, 3.2)
0.17	-0.6	-1.2	0.7	(-1.2, 2.6)	(-1.7, 3.1)
0.33	-0.5	-0.9	0.5	(-1.4, 2.4)	(-1.9, 3.0)
0.67	4.9	-1.2	6.3	(4.5, 8.2)	(3.9, 8.8)
1	5.7	-2.4	8.3	(6.5, 10.2)	(5.9, 10.8)
2	5.1	-4.1	9.3	(7.4, 11.2)	(6.9, 11.7)
3	5.5	-2.9	8.7	(6.9, 10.6)	(6.3, 11.2)
5	3.0	-1.5	4.9	(3.0, 6.7)	(2.4, 7.3)
8	-0.7	-6.5	6.1	(4.3, 8.0)	(3.7, 8.6)
12	-0.1	-6.0	6.1	(4.2, 8.0)	(3.7, 8.5)
24	-3.3	-6.0	2.9	(1.0, 4.8)	(0.4, 5.3)

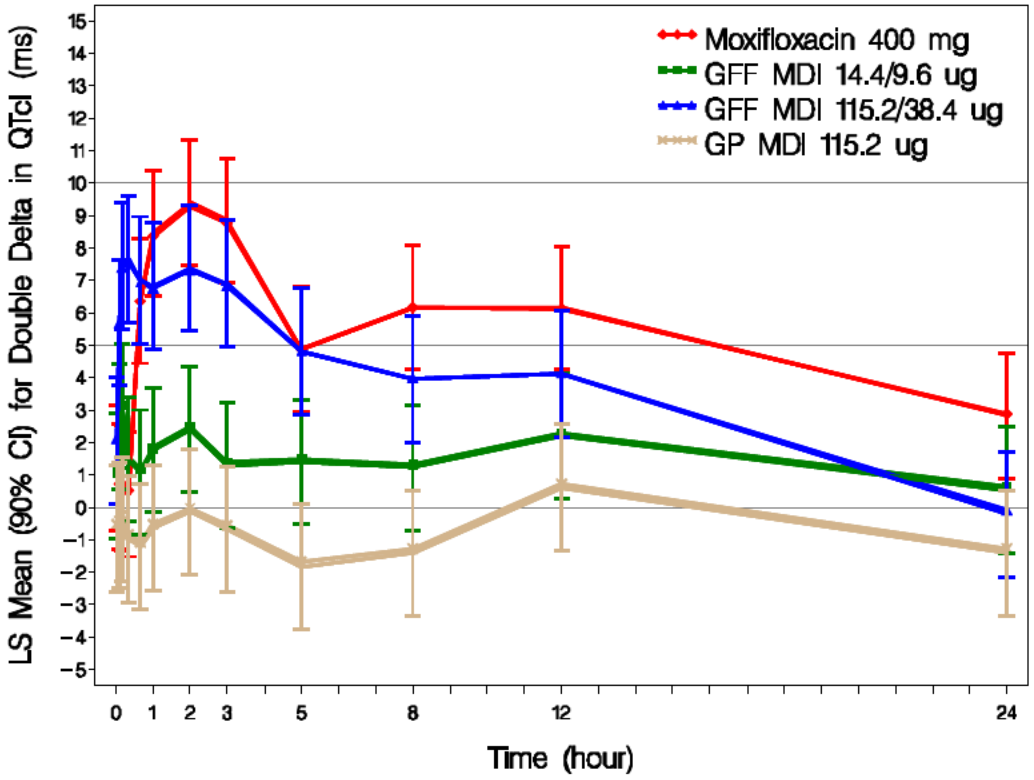
* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 5: Mean and 90% CI ΔΔQTcI Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcI values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 10: Categorical Analysis for QTcI

	Total N		QTcI<=450 ms		450<QTcI<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	69	968	69 (100%)	968 (100%)	0 (0.0%)	0 (0.0%)
Placebo MDI	63	752	63 (100%)	752 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	67	787	66 (98.5%)	786 (99.9%)	1 (1.5%)	1 (0.1%)
GFF MDI 14.4/9.6 µg	66	786	65 (98.5%)	785 (99.9%)	1 (1.5%)	1 (0.1%)
GFF MDI 115.2/38.4 µg	64	749	61 (95.3%)	744 (99.3%)	3 (4.7%)	5 (0.7%)
GP MDI 115.2 µg	65	777	64 (98.5%)	776 (99.9%)	1 (1.5%)	1 (0.1%)

Table 11 lists the categorical analysis results for ΔQTcI. No subject's change from baseline in QTcI was above 60 ms.

Table 11: Categorical Analysis of ΔQTcI

	Total N		ΔQTcI<=30 ms		30<ΔQTcI<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Placebo MDI	63	752	61 (96.8%)	750 (99.7%)	2 (3.2%)	2 (0.3%)
Moxifloxacin 400 mg	67	787	65 (97.0%)	785 (99.7%)	2 (3.0%)	2 (0.3%)
GFF MDI 14.4/9.6 µg	66	786	66 (100%)	786 (100%)	0 (0.0%)	0 (0.0%)
GFF MDI 115.2/38.4 µg	63	744	61 (96.8%)	740 (99.5%)	2 (3.2%)	4 (0.5%)
GP MDI 115.2 µg	65	777	63 (96.9%)	775 (99.7%)	2 (3.1%)	2 (0.3%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between GFFMDI 14.4/9.6 µg and placebo and GFF MDI 115.2/38.4 µg and placebo were 5.0 bpm and 8.6 bpm, respectively.

The outlier analysis results for HR are presented in Table 13.

Table 12: Analysis Results of ΔHR and ΔΔHR

		GFF MDI 14.4/ 9.6 µg		GFF MDI 115.2/ 38.4 µg		GP MDI 115.2 µg	
		ΔHR (bpm)	ΔΔHR (bpm)	ΔHR (bpm)	ΔΔHR (bpm)	ΔHR (bpm)	ΔΔHR (bpm)
Time (hour)	ΔHR (bpm) Placebo	LSmean	LSmean (90% CI)	LSmean	LSmean (90% CI)	LSmean	LSmean (90% CI)
0.03	5.6	6.7	1.5 (0.0, 3.0)	9.2	3.8 (2.2, 5.3)	6.2	0.9 (-0.6, 2.4)
0.1	1.1	4.1	3.5 (2.0, 5.0)	7.8	6.8 (5.3, 8.3)	1.6	0.8 (-0.7, 2.3)
0.17	1.2	4.0	3.1 (1.7, 4.6)	8.3	7.0 (5.5, 8.5)	1.3	0.3 (-1.2, 1.8)
0.33	1.0	3.4	2.8 (1.4, 4.3)	6.4	5.5 (3.9, 7.0)	0.8	0.1 (-1.4, 1.6)
0.67	0.4	2.5	2.5 (1.0, 4.0)	7.0	6.7 (5.2, 8.2)	1.0	0.8 (-0.7, 2.3)
1	0.7	3.1	2.9 (1.4, 4.3)	7.6	7.0 (5.5, 8.6)	1.2	0.7 (-0.8, 2.2)
2	1.9	3.2	1.7 (0.2, 3.2)	8.1	6.2 (4.7, 7.7)	0.4	-1.3 (-2.8, 0.2)
3	0.6	2.0	1.8 (0.3, 3.3)	6.1	5.6 (4.1, 7.1)	-0.2	-0.5 (-2.0, 1.0)
5	11.1	11.4	0.7 (-0.8, 2.1)	14.0	3.3 (1.8, 4.8)	9.0	-1.8 (-3.3, -0.3)
8	10.2	9.5	-0.3 (-1.8, 1.2)	13.3	3.2 (1.7, 4.7)	7.5	-2.4 (-3.9, -1.0)
12	8.0	8.2	0.7 (-0.8, 2.2)	10.3	2.5 (0.9, 4.0)	6.1	-1.6 (-3.1, -0.1)
24	9.6	10.7	1.6 (0.1, 3.0)	12.4	2.9 (1.4, 4.4)	9.6	0.2 (-1.2, 1.7)

Table 13: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline	69	69 (100%)	0 (0.0%)	65 (94.2%)	4 (5.8%)
Placebo MDI	63	61 (96.8%)	2 (3.2%)	61 (96.8%)	2 (3.2%)
Moxifloxacin 400 mg	67	64 (95.5%)	3 (4.5%)	66 (98.5%)	1 (1.5%)
GFF MDI 14.4/9.6 µg	66	66 (100%)	0 (0.0%)	66 (100%)	0 (0.0%)
GFF MDI 115.2/38.4 µg	66	64 (97.0%)	2 (3.0%)	66 (100%)	0 (0.0%)
GP MDI 115.2 µg	66	65 (98.5%)	1 (1.5%)	65 (98.5%)	1 (1.5%)

5.2.3 PR Analysis

Similar statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the PR mean differences between GFFMDI 14.4/9.6 µg and placebo and GFF MDI 115.2/38.4 µg and placebo were 3.1 ms and 2.7 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

Table 14: Analysis Results of ΔPR and ΔΔPR

		GFF MDI 14.4/ 9.6 µg		**GFF MDI 115.2/ 38.4 µg**		**GP MDI 115.2 µg**	
		ΔPR (ms)	**ΔΔPR (ms)**	**ΔPR (ms)**	**ΔΔPR (ms)**	**ΔPR (ms)**	**ΔΔPR (ms)**
Time (hour)	**ΔPR (ms) Placebo**	**LSmean**	**LSmean (90% CI)**	**LSmean**	**LSmean (90% CI)**	**LSmean**	**LSmean (90% CI)**
0.03	-5.7	-6.0	-0.3 (-2.6, 2.0)	-5.8	0.0 (-2.2, 2.3)	-5.5	-0.0 (-2.3, 2.2)
0.1	-2.9	-4.2	-1.4 (-3.6, 0.9)	-7.3	-4.3 (-6.6, -2.0)	-2.9	-0.3 (-2.5, 2.0)
0.17	-3.0	-3.5	-0.6 (-2.8, 1.7)	-8.4	-5.3 (-7.6, -3.0)	-1.5	1.3 (-0.9, 3.6)
0.33	-2.0	-3.8	-1.8 (-4.0, 0.5)	-8.7	-6.6 (-8.9, -4.4)	-0.3	1.5 (-0.8, 3.8)
0.67	-1.7	-2.8	-1.1 (-3.3, 1.2)	-6.8	-5.0 (-7.2, -2.7)	-0.9	0.7 (-1.6, 2.9)
1	-0.7	-2.6	-2.0 (-4.2, 0.3)	-5.9	-5.1 (-7.4, -2.8)	-0.0	0.5 (-1.8, 2.7)
2	0.3	0.5	0.2 (-2.1, 2.4)	-3.6	-3.7 (-6.0, -1.5)	0.8	0.3 (-2.0, 2.6)
3	-3.4	-4.7	-1.5 (-3.7, 0.8)	-7.2	-3.7 (-6.0, -1.4)	-3.6	-0.4 (-2.6, 1.9)
5	-8.7	-8.4	0.2 (-2.1, 2.4)	-10.9	-2.1 (-4.4, 0.2)	-8.6	-0.1 (-2.4, 2.1)
8	-9.1	-8.8	0.1 (-2.2, 2.3)	-9.9	-0.7 (-3.0, 1.6)	-7.3	1.6 (-0.7, 3.9)
12	-8.9	-10.3	-1.4 (-3.6, 0.8)	-8.4	0.4 (-1.9, 2.7)	-7.6	1.1 (-1.2, 3.4)
24	-3.0	-2.1	0.9 (-1.4, 3.1)	-4.0	-0.8 (-3.1, 1.4)	-3.1	-0.3 (-2.6, 2.0)

Table 15: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline	68	953	62 (91.2%)	917 (96.2%)	6 (8.8%)	36 (3.8%)
Placebo MDI	63	746	59 (93.7%)	741 (99.3%)	4 (6.3%)	5 (0.7%)
Moxifloxacin 400 mg	67	784	63 (94.0%)	763 (97.3%)	4 (6.0%)	21 (2.7%)
GFF MDI 14.4/9.6 µg	66	778	61 (92.4%)	757 (97.3%)	5 (7.6%)	21 (2.7%)
GFF MDI 115.2/38.4 µg	66	748	63 (95.5%)	741 (99.1%)	3 (4.5%)	7 (0.9%)
GP MDI 115.2 µg	66	773	62 (93.9%)	760 (98.3%)	4 (6.1%)	13 (1.7%)

5.2.4 QRS Analysis

Similar statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the QRS mean differences between GFFMDI 14.4/9.6 µg and placebo and GFF MDI 115.2/38.4 µg and placebo were 0.8 ms and 1.4 ms, respectively.

The outlier analysis results for QRS are presented in Table 17.

Table 16: Analysis Results of ΔQRS and ΔΔQRS

		GFF MDI 14.4/ 9.6 µg		GFF MDI 115.2/ 38.4 µg		GP MDI 115.2 µg	
		ΔQRS (ms)	ΔΔQRS (ms)	ΔQRS (ms)	ΔΔQRS (ms)	ΔQRS (ms)	ΔΔQRS (ms)
Time (hour)	ΔQRS (ms) Placebo	LSmean	LSmean (90% CI)	LSmean	LSmean (90% CI)	LSmean	LSmean (90% CI)
0.03	-0.2	-0.0	0.2 (-0.3, 0.7)	-0.2	-0.0 (-0.6, 0.5)	-0.1	0.1 (-0.5, 0.6)
0.1	-0.1	0.2	0.3 (-0.2, 0.8)	0.1	0.2 (-0.3, 0.7)	0.0	0.1 (-0.4, 0.6)
0.17	0.0	0.1	0.1 (-0.4, 0.6)	0.2	0.1 (-0.4, 0.6)	0.0	0.0 (-0.5, 0.5)
0.33	-0.0	0.2	0.2 (-0.3, 0.7)	0.4	0.4 (-0.1, 0.9)	0.1	0.2 (-0.3, 0.7)
0.67	0.0	0.2	0.2 (-0.3, 0.7)	0.7	0.6 (0.1, 1.1)	0.2	0.2 (-0.3, 0.7)
1	-0.0	0.2	0.2 (-0.3, 0.7)	0.8	0.7 (0.2, 1.3)	0.2	0.3 (-0.2, 0.8)
2	-3.3	-3.1	0.2 (-0.3, 0.7)	-2.4	0.9 (0.4, 1.4)	-3.4	-0.0 (-0.5, 0.5)
3	0.1	0.3	0.2 (-0.3, 0.7)	0.5	0.4 (-0.1, 0.9)	0.2	0.2 (-0.3, 0.7)
5	0.6	0.9	0.2 (-0.3, 0.7)	1.1	0.4 (-0.1, 0.9)	0.6	-0.1 (-0.6, 0.4)
8	-3.8	-3.9	-0.1 (-0.6, 0.4)	-3.9	-0.1 (-0.6, 0.4)	-4.0	-0.2 (-0.7, 0.3)
12	-0.1	0.1	0.2 (-0.3, 0.7)	0.1	0.2 (-0.3, 0.8)	-0.0	0.1 (-0.4, 0.6)
24	-3.3	-3.3	0.0 (-0.5, 0.5)	-3.2	0.0 (-0.5, 0.6)	-3.3	0.0 (-0.5, 0.5)

Table 17: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	69	968	56 (81.2%)	852 (88.0%)	13 (18.8%)	116 (12.0%)
Placebo MDI	63	753	53 (84.1%)	682 (90.6%)	10 (15.9%)	71 (9.4%)
Moxifloxacin 400 mg	67	793	53 (79.1%)	693 (87.4%)	14 (20.9%)	100 (12.6%)
GFF MDI 14.4/9.6 µg	66	788	56 (84.8%)	717 (91.0%)	10 (15.2%)	71 (9.0%)
GFF MDI 115.2/38.4 µg	66	758	50 (75.8%)	647 (85.4%)	16 (24.2%)	111 (14.6%)

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
GP MDI 115.2 µg	66	782	53 (80.3%)	701 (89.6%)	13 (19.7%)	81 (10.4%)

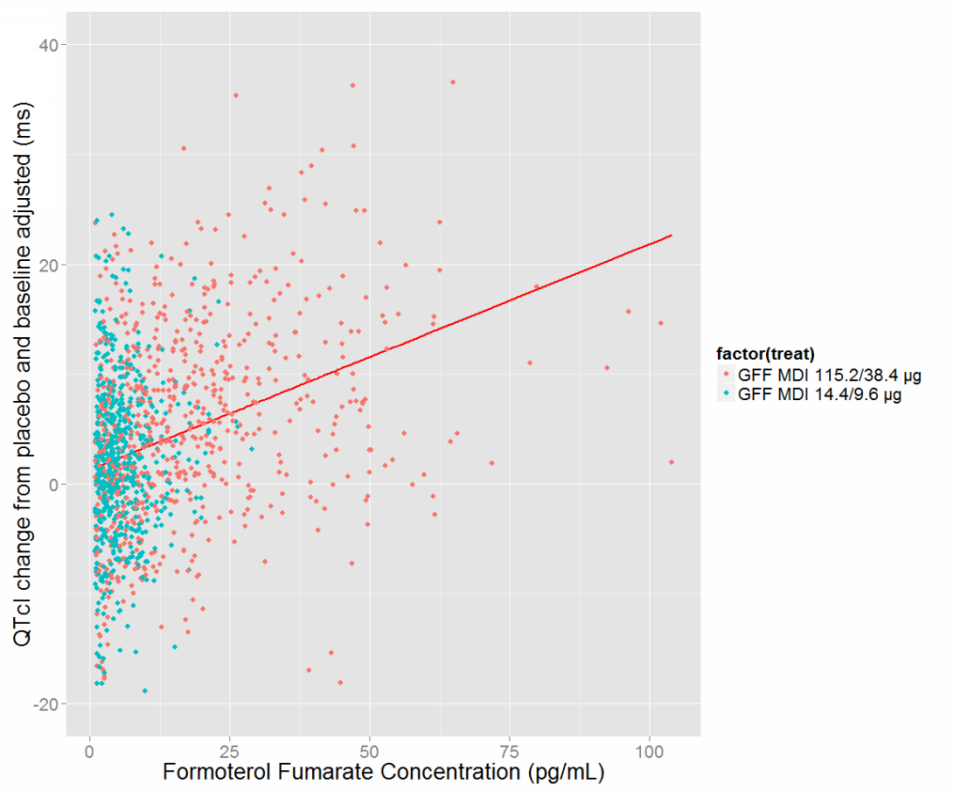
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔΔQTcI and and formoterol fumarate concentrations is shown in Table 18 and visualized in Figure 6, with significant exposure-response relationship (P<0.0001).

Table 18: Exposure- ΔΔQTcI Analysis for Formoterol

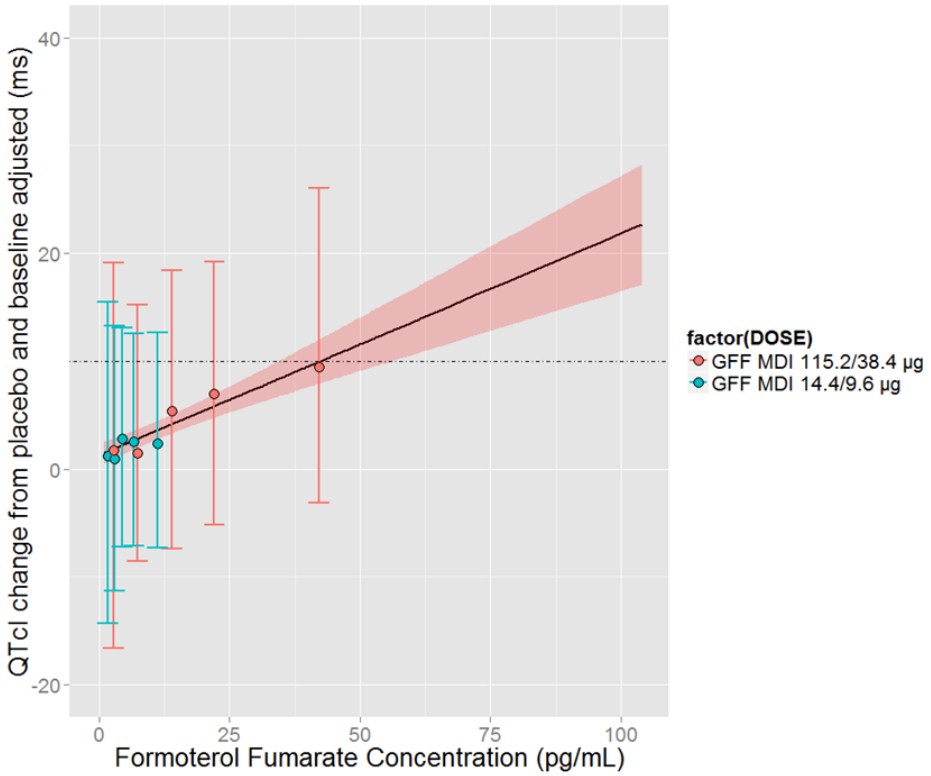
Parameter	Estimate	P-value	*Inter-individual Variability*
ΔΔQTcI = Intercept + slope *Formoterol Concentration			
Intercept (ms)	1.257	0.05	4.565
Slope (ms per ng/mL)	0.206	<0.0001	0.224
Residual Variability (ms)	6.883		

Figure 6: Observed ΔΔQTcI vs Formoterol Fumarate Concentrations Together with the Population Predictions (solid red line)



The goodness-of-fit plot in Figure 7 shows the observed median-quantile of Formoterol Fumarate concentrations and associated mean (90% CI) ΔΔQTcI together with the mean (90% CI) predicted ΔΔQTcI.

Figure 7: Observed Median-Quantile Formoterol Fumarate Concentration and Associated Mean (90% CI) ΔΔQTcI (colored dots) Together with the Mean (90% CI) Predicted ΔΔQTcI (black line with shaded red area)

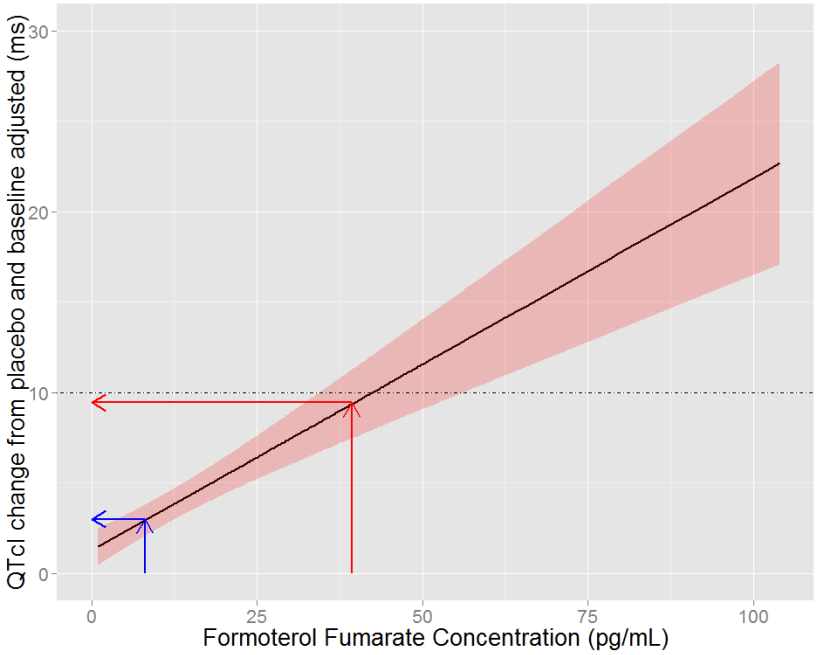


The predicted ΔΔQTcIs at the geometric mean peak concentrations of Formoterol Fumarate for 115.2/38.4 µg and 14.4/9.6 µg are shown in Table 19 and visualized in Figure 8. A marginal QTc prolongation could be expected at the geometric mean formoterol plasma concentration after a supra-therapeutic dose of 38.4 µg FF.

Table 19: Predicted ΔΔQTcI Interval at Geometric Mean Peak Formoterol Fumarate Concentration

Treatment	Cmax	Prediced ΔΔQTcI	90% CI
GFF 115.2/38.4 µg	*39.31 pg/mL*	*9.38*	*(7.47; 11.28)*
GFF 14.4/9.6 µg	*8.06 pg/mL*	*2.92*	*(2.05; 3.78)*

Figure 8: Mean (90% CI) Predicted ΔΔQTcI at Geometric Mean Cmax.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

One subject withdrew for PR prolongation, but there did not seem to be any clinically significant systematic effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology and Cardiac Safety

1.	Therapeutic dose (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses)	The maximum proposed clinical dosing regimen will be GP MDI 18 µg BID, and GFF MDI 18/9.6 µg, and FF MDI 9.6 µg.
2.	Maximum tolerated dose (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses)	Not identified. GFF MDI 144 /38.4 µg, GP MDI 144 µg and FF MDI 19.2 µg were the highest doses studied and were tolerated.
3.	Principal adverse events	Below is a summary of principal adverse events in Phase 1 studies: In Study PT010001, the most frequently reported TEAE among the 78 subjects who received GFF MDI 14.4/9.6 µg was hypokalemia, which was reported by 3 subjects (3.8%). In Study PT0010801, of 33 subjects enrolled and treated with at least 1 dose of study drug the most frequently reported TEAE was dry mouth, reported by 4.8%, 14.3%, 0, and 4.8% of subjects exposed to GP MDI 144 µg, 72 µg, 36 µg, and 18 µg, respectively, 9.5% of subjects exposed to Placebo MDI, and 9.1% of subjects exposed to Spiriva. In Study PT0050801, of the 34 subjects enrolled and treated with at least 1 dose of study drug, headache was the most frequently reported TEAE (5 events following FF MDI 2.4 µg, 1 following FF MDI 9.6 µg, 2 following Foradil, and 2 following Placebo MDI) followed by dyspnea (1 event following FF MDI 2.4 µg, 1 following FF MDI 4.8 µg, 1 following Foradil, and 2 following Placebo MDI). In Study PT005003, of the 50 subjects enrolled and treated with at least 1 dose of study drug the most frequently reported TEAEs were tremor and nasopharyngitis, each reported in 2 subjects (4.0%) overall; tremor was reported in 1 subject while receiving FF MDI 19.2 µg and again while receiving Foradil 12 µg, and in another subject while receiving Foradil 12 µg; nasopharyngitis was reported in 2 subjects receiving Foradil 24 µg. In Study PT0030901, of the 16 subjects enrolled and treated with at least 1 dose of study drug, the most frequently reported TEAEs were headache (reported for 33% of subjects following GFF MDI and ≤13% following the other treatments) and dry mouth (13% to 27% across the 4 treatments). In Study PT003009, of the 69 subjects enrolled and treated with at least 1 dose of study drug, the incidence of TEAEs

		for each of the 4 active treatments, regardless of relationship to study drug never exceeded the incidence observed for placebo MDI and the incidence of treatment-related TEAEs for each of the 4 active treatments was slightly less than the incidence for placebo MDI. In Study PT003010, of the 24 subject enrolled and treated with at least 1 dose of study drug, treatment-emergent AEs reported by Preferred Term that occurred in ≥2 subjects overall included dizziness, headache, and anemia (4 subjects [16.7%] each), injection site pain and dysmenorrhea (3 subjects [12.5%] each), and somnolence (2 subjects [8.3%]). Below is a summary of principal adverse events based on the integrated analysis of Phase IIb chronic dosing studies (Studies PT001002, PT001003, PT0031002, PT003003, PT003004, and PT003005): The incidence rate of AEs was highest among patients receiving GFF MDI 72/9.6 µg. The lowest incidence of AE's within the GFF MDI treatments occurred in patients receiving GFF MDI 1.2/9.6 µg (14.7%) followed by GFF MDI 18/9.6 µg (23.4%). The incidence rate of AEs in patients treated with GP MDI was highest in patients treated with GP MDI 36 µg. There did not appear to be a dose ordering for GP MDI doses between 18 and 0.6 µg and the incidence rate of AEs in this range of doses was lower than in patients receiving Spiriva or Atrovent. The incidence of AEs in patients treated with FF MDI was comparable to and slightly lower than patients treated with Foradil Aerolizer. The most frequently reported AE within all of the treatments was dry mouth, with the highest incidence occurring in patients treated with GFF MDI 72/9.6 µg. The most frequently reported TEAEs (those reported in ≥3% of subjects during any treatment) within the first 7 days of each treatment period were compared for subjects treated with GFF MDI, GP MDI, and FF MDI. The most frequently reported TEAE over 7 days across all treatments was dry mouth in 6.6%, 8.0%, and 5.3% of subjects treated with GFF MDI, GP MDI, and FF MDI overall, respectively, compared with 4.7%, 2.1%, 3.5%, and 2.5% in subjects treated with Spiriva, Atrovent, Foradil

		Aerolizer, and Placebo MDI, respectively. The second most frequently reported TEAE across all treatments was headache in 2.7%, 0.9%, and 0.4% of subjects during treatment with GFF MDI, GP MDI, and FF MDI, respectively; there was no apparent evidence of dose ordering across the individual doses. The third most frequently reported TEAE was tremor in 3.2% of subjects treated with GFF MDI and 3.6% of subjects treated with FF MDI; there was no apparent dose ordering across individual GFF MDI doses. Below is a summary of principal adverse events based on the integrated Phase III Pivotal 24-Week Studies (Studies PT003006 and PT003007): Across treatment groups, the most frequently reported TEAEs by Preferred Term were nasopharyngitis, upper respiratory tract infection, and cough; the incidences of these events in the GFF MDI 14.4/9.6 µg, FF MDI 9.6 µg, and GP MDI 14.4 µg groups were generally similar to or lower than the incidences in the Placebo MDI and Spiriva 18 µg groups. The most commonly reported TEAEs in the GFF MDI 14.4/9.6 µg group that occurred at higher incidences (at least 1 percentage point higher) compared with the Placebo MDI group were cough (4.0% vs 2.7%, respectively) and dry mouth (1.3% vs 0.2%, respectively), although the differences in incidence were small (<2%). The incidences of the most common TEAEs in the GFF MDI 14.4/9.6 µg group were generally similar to the incidences in the FF MDI 9.6 µg and GP MDI 14.4 µg individual component groups and the Spiriva 18 µg group, with differences between groups generally being 1% to 2%. Below is a summary of principal adverse events based on the integrated Phase III Pivotal and Long-Term Studies (Studies PT003006, PT003007 and PT003008) during 52 weeks of treatment: The most commonly reported TEAEs (in ≥3.0% of subjects) in the GFF MDI 14.4/9.6 µg group were nasopharyngitis (6.8%), cough (4.2%), upper respiratory tract infection (3.8%), urinary tract infection (UTI; 3.5%), COPD (includes COPD exacerbations and COPD worsening; 3.2%), and sinusitis (3.2%). The incidences of the most common TEAEs in the GFF MDI 14.4/9.6 µg group were generally similar in the FF MDI 9.6 µg and GP

		MDI 14.4 µg individual component groups and the Spiriva 18 µg group, with the exception of a lower incidence of nasopharyngitis in the GP MDI 14.4 µg group (GFF MDI 14.4/9.6 µg: 6.8%, FF MDI 9.6 µg: 6.2%, GP MDI 14.4 µg: 4.3%, Spiriva 18 µg: 6.2%) and a higher incidence of gastroesophageal reflux disease (GERD) in the Spiriva 18 µg group (GFF MDI 14.4/9.6 µg: 0.9%, FF MDI 9.6 µg: 0.7%, GP MDI14.4 µg: 1.0%, Spiriva 18 µg: 3.1%).	
4.	Maximum dose tested (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses)	Single Dose	GFF MDI 144 /38.4 µg GP MDI 144 µg FF MDI 19.2 µg
		Multiple Dose	GFF MDI 72/9.6 µg BID x7 days (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses): GP MDI 36 µg BID x7 days (i.e., 36 µg glycopyrrolate, equivalent to 28.8 µg glycopyrronium) FF MDI 9.6 µg BID x24 weeks
5.	Exposures Achieved at Maximum Tested Dose (Glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses)	Single Dose	Mean (±SD) were as follows: GFF MDI 144/38.4 µg: ○ Glycopyrronium=105 (±156) pg/mL for C_{max} and was 179 (±102) pg.h/mL for AUC_{0-12} ○ FF = 39.4 (±21.8) pg/mL for C_{max} and was 148 (±59.0) pg.h/mL for AUC_{0-12} • GP MDI 144 µg: 160 (±118) pg/mL for C_{max} and AUC_{0-12} was 398 (±318) pg.h/mL. • FF MDI 19.2 µg: 21.2 (±10.1) pg/mL for C_{max} and AUC_{0-12} was 107 (±40.6) pg.h/mL
		Multiple Dose	Mean (±SD) were as follows: GFF MDI 72/9.6 µg BID x7 days (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses): ○ Glycopyrronium= 179 (±161) pg/mL for C_{max} and was 605 (±345) pg.h/mL for AUC_{0-12} ○ FF = 18.2 (±10.2) pg/mL for C_{max} and was 115 (±58.3) pg.h/mL for AUC_{0-12} • GP MDI 36 µg BID x7 days: 98.2 (67.0) pg/mL for C_{max} and was 357 (205) pg.h/mL for AUC_{0-12}

			• FF MDI 9.6 µg BID x24 weeks: 12.3 (6.12) pg/mL for C_{max} and was 75.7 (44.4) pg.h/mL for AUC_{0-12}
6.	Range of linear PK (glycopyrrolate doses expressed; refer to Table 2 for glycopyrronium equivalent doses):	The systemic exposure of glycopyrronium increased generally in proportion to the dose. There was a slight departure from dose linearity at the highest dose level (144 µg glycopyrrolate, equivalent to 115.2 µg of glycopyrronium) according to the population PK model. Systemic exposure to formoterol from FF MDI demonstrated a clear linear relationship across the single dosage range (2.4 µg to 19.2 µg formoterol fumarate).	
7.	Accumulation at steady state (glycopyrronium doses expressed; refer to Table 2 for glycopyrrolate equivalent doses):	PT003006: • Glycopyrronium accumulation ratios following GFF MDI 14.4/9.6 µg chronic dosing were 2.30 [90% CIs: 2.04, 2.59] based on AUC_{0-12} and 1.40 [90% CIs: 1.22, 1.59] based on C_{max}. • Glycopyrronium accumulation ratios following GP MDI 14.4 µg chronic dosing were 2.00 [90% CIs: 1.65, 2.42] based on AUC_{0-12} and 1.26 [1.06, 1.50] based on Cmax. • Formoterol accumulation ratios following GFF MDI 14.4/9.6 µg chronic dosing were 1.52 [1.36, 1.69] based on AUC_{0-12} and 1.31 [1.21, 1.43] based on C_{max}. • Formoterol accumulation ratios following FF MDI 9.6 µg chronic dosing were 1.62 [1.41, 1.86] based on AUC_{0-12} and 1.51 [1.34, 1.71] based on C_{max}.	
8.	Metabolites	N/A for glycopyrronium; the primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.	
9.	Absorption (glycopyrronium doses expressed; refer to Table 2 for glycopyrrolate equivalent doses):	Absolute/Relative Bioavailability	N/A
		Tmax	***Glycopyrronium:*** Following inhaled administration of GFF MDI at the recommended dose in subjects with COPD, peak concentrations occurred at 5 minutes. Across the range of doses tested: • Median t_{max} ranged from 0.06 to 0.100 h (minimum: 0.03 h; maximum: 8.00 h) for single dose

			GFF MDI 14.4/9.6 µg to GFF MDI 115.2/38.4 µg • Median t_{max} ranged from 0.083 to 0.100 h (minimum: 0.00 h; maximum: 7.93 h) for multiple dose GFF MDI 14.4/9.6 µg to GFF MDI 72/9.6 µg BID • Median t_{max} ranged from 0.07 to 0.333 h (minimum: 0.033 h; maximum: 5.00 h) for single dose GP MDI 14.4 µg to GP MDI 115.2 µg • Median t_{max} ranged from 0.083 to 0.100 h (minimum: 0.00 h; maximum: 12.00 h) for multiple dose GP MDI 14.4 µg to GP MDI 36 µg ***Formoterol:*** Following inhaled administration of GFF MDI at the recommended dose in subjects with COPD, peak concentrations occurred within 20 to 60 minutes. Across the range of doses tested: • Median t_{max} ranged from 0.10 to 0.583 h (minimum: 0.03 h; maximum: 8.00 h) for single dose GFF MDI 14.4/9.6 µg to GFF MDI 115.2/38.4 µg • Median t_{max} ranged from 0.367 to 1.01 h (minimum: 0.03 h; maximum: 9.97 h) for multiple dose GFF MDI 14.4/9.6 µg to GFF MDI 72/9.6 µg BID • Median t_{max} ranged from 0.08 to 1.42 h (minimum: 0.033; maximum: 12.0) for single dose FF MDI 2.4 µg to FF MDI 19.2 µg • Median t_{max} ranged from 0.917 to 0.983 h (minimum: 0.033 h; maximum: 9.92 h) for multiple dose FF MDI 7.2 µg to FF MDI 9.6 µg
10.	Distribution	Vc/F	• Typical Vc/F and V2/F of glycopyrronium were 951 L and 2019 L, respectively for

			glycopyrronium • Typical Vc/F and V2/F of formoterol were 948 L and 434 L, respectively
		% bound	N/A for glycopyrronium; 46% and 58% for formoterol based on Symbicort MDI PI.
11.	Elimination	Route	In both urine and bile, > 80% of the radioactivity corresponded to unchanged drug and 5 to 15% as the alkaline hydrolysate of glycopyrronium (Kaltiala, 1974)
		Terminal t½	Based on the population PK model, the terminal elimination half-lives of glycopyrronium and formoterol were both 11.8 hours.
		CL/F or CL	• The typical CL/F of glycopyrronium was 217 L/h (i.e., 3.6 L/min). • The typical CL/F of formoterol was 102 L/h (i.e., 1.7 L/min).
12.	Intrinsic Factors	Age	The final population PK model of glycopyrronium included an effect of age on Ka power function of -2.44 $[(Age/62)^{-2.44}]$, and CL/F with a power function of -1.33 $[(Age/62)^{-1.33}]$. Based on this model, the Ka of glycopyrronium in typical 79-year old subject would be ~45% lower than in a typical 62 year old subject. The CL/F of glycopyrronium in a typical 40 and 79-year old subject would be expected to be approximately 79% higher and 28% lower relative to a typical 62-year old subject, respectively.
		Sex	Sex was not an identified as significant covariates explaining the variability of PK parameters of glycopyrronium and formoterol. Of note, the mean effect of sex on glycopyrronium CL/F was a 16% increase in clearance for men relative to women and was not statistically significant (p-value = 0.1768). The mean effect of sex on formoterol CL/F was an 11% increase in clearance for men relative to women and was not statistically significant (p-value = 0.1276).

			excretion. Based on the final population PK model, glycopyrronium CL/F was found to be dependent on baseline creatinine clearance. The power function of baseline creatinine clearance (CRCLBSLC) on CL/F was 0.250 [(CRCLBSLC/94.2)$^{0.250}$]. The typical CL/F of glycopyrronium in patients with moderate renal impairment (45 mL/min creatinine clearance) is expected to be approximately 17% lower than subjects with normal renal function (creatinine clearance of 94.2 mL/min). • Specific pharmacokinetic information in patients with hepatic impairment with formoterol fumarate is not available, however formoterol is primarily eliminated via hepatic metabolism, thus an increased exposure can be expected in subjects with severe liver impairment. Based on the final population PK model, formoterol CL/F was found to be dependent on baseline creatinine clearance (CRCLBSLC). The power function of baseline creatinine clearance on CL/F was 0.502 [(CRCLBSLC/94.0)$^{0.502}$]. Based on this model, the CL/F of formoterol in patients with moderate renal impairment (45 mL/min creatinine clearance) is expected to be approximately 31% slower than subjects with normal renal function (creatinine clearance of 94 mL/min).
13.	Extrinsic Factors	Drug interactions	No interaction was detected following co-administration of glycopyrronium and formoterol fumarate based on studies conducted in healthy and COPD subjects. According to the population model, when given as GFF MDI the mean apparent oral plasma clearance of glycopyrronium was

			statistically significant compared to when given as GP MDI (monoproduct) but only 18% higher, according to the population model. Thus, co-administration with formoterol fumarate as the fixed combination GFF MDI did not result in a clinically relevant effect on the PK parameters of glycopyrronium. Also, based on the PK model, the Vc/F of glycopyrronium and formoterol were dependent on the use of ICS. The typical Vc/F of glycopyrronium in subjects taking ICS at baseline was 36% (RSE of 19.2%) larger than subjects who did not take ICS. The typical Vc/F of formoterol in subjects taking ICS at baseline was 32% (RSE of 14.5%) larger than subjects who did not take ICS.
		Food Effects	N/A
14.	Expected High Clinical Exposure Scenario	Following a dose of GFF MDI 18/9.6 µg, the predicted glycopyrronium $AUC_{0\text{-}12,ss}$ for a 90-year old subject with moderate renal impairment (CrCL=50 mL/min) is 128 pg*h/mL (1.9-fold higher than the reference $AUC_{0\text{-}12\ ss}$ of 66.4 pg*h/mL based on a subject of 62 years old and CrCL=94.2 mL/min; Figure 3). In a 90-year old subject with severe renal impairment (CrCL=25 mL/min), the predicted glycopyrronium $AUC_{0\text{-}12,\ ss}$ is 152 pg*h/mL (2.3-fold higher than the reference $AUC_{0\text{-}12\ ss}$). Following a dose of GFF MDI 18/9.6 µg, the predicted formoterol $AUC_{0\text{-}12\ ss}$ for a subject with post-ventolin FEV_1 of 0.64 L and moderate renal impairment (CrCL=50 mL/min) is 168 pg*h/mL (1.8-fold higher than the reference $AUC_{0\text{-}12\ ss}$ of 94.1 pg*h/mL based on a subject post-ventolin FEV_1 of 1.52 L and CrCL=94.0 mL/min; Figure 4). In a subject with post-ventolin FEV_1 of 0.64 L with severe renal impairment (CrCL= 25 mL/min), the predicted formoterol $AUC_{0\text{-}12\ ss}$ is 238 pg*h/mL (2.5-fold higher than the reference $AUC_{0\text{-}12\ ss}$).	
15.	Preclinical Cardiac Safety	There were no *in vitro* studies conducted. Overall, the results of the rat and dog inhalation toxicology studies support the presumption that GFF MDI yields no significant toxicity other than cardiac alterations (i.e. increased heart rate) previously reported for formoterol	

		fumarate-containing approved drugs such as Symbicort® MDI. The cardiac findings observed in the 14-day studies were not present in the 3-month dog study with either GFF MDI or FF MDI, suggesting that the cardiac findings were temporary adaptations which subsided upon longer term exposure. The GP MDI studies that dosed up to 6 months in dogs and rats had no significant observations, and the FF MDI studies up to 3 months in dogs had similar profiles to the GFF MDI studies and other formoterol fumarate-containing approved drugs. Additionally, no new, unusual, or interactive adverse effects were observed compared to the previous animal inhalation studies. See Section 2.6.6 Toxicology Written Summary for further details.
16.	Clinical Cardiac Safety (glycopyrronium doses expressed; refer to Table 2 for glycopyrrolate equivalent doses):	Below is a summary of principal adverse events in Phase 1 studies: In Study PT010001, the most frequently reported TEAE among the 78 subjects who received GFF MDI 14.4/9.6 µg was hypokalemia, which was reported by 3 subjects (3.8%). In Study PT0010801, of 33 subjects enrolled and treated with at least 1 dose of study drug the most frequently reported TEAE was dry mouth, reported by 4.8%, 14.3%, 0, and 4.8% of subjects exposed to GP MDI 144 µg, 72 µg, 36 µg, and 18 µg, respectively, 9.5% of subjects exposed to Placebo MDI, and 9.1% of subjects exposed to Spiriva. In Study PT0050801, of the 34 subjects enrolled and treated with at least 1 dose of study drug, headache was the most frequently reported TEAE (5 events following FF MDI 2.4 µg, 1 following FF MDI 9.6 µg, 2 following Foradil, and 2 following Placebo MDI) followed by dyspnea (1 event following FF MDI 2.4 µg, 1 following FF MDI 4.8 µg, 1 following Foradil, and 2 following Placebo MDI). In Study PT005003, of the 50 subjects enrolled and treated with at least 1 dose of study drug the most frequently reported TEAEs were tremor and nasopharyngitis, each reported in 2 subjects (4.0%) overall; tremor was reported in 1 subject while receiving FF MDI 19.2 µg and again while receiving Foradil 12 µg, and in another subject while receiving Foradil 12 µg; nasopharyngitis was reported in 2 subjects receiving Foradil 24 µg. In Study PT0030901, of the 16 subjects enrolled and treated with at least 1 dose of study drug, the most frequently reported TEAEs were headache (reported for 33% of subjects following GFF MDI and ≤13% following the other treatments) and dry mouth (13% to 27% across the 4

		treatments). In Study PT003009, of the 69 subjects enrolled and treated with at least 1 dose of study drug, the incidence of TEAEs for each of the 4 active treatments, regardless of relationship to study drug never exceeded the incidence observed for placebo MDI and the incidence of treatment-related TEAEs for each of the 4 active treatments was slightly less than the incidence for placebo MDI. The largest mean (95% upper confidence bound) differences from placebo in baseline-corrected QTcI for GFF MDI 14.4/9.6 µg and GFF MDI 115.2/38.4 µg (i.e., 115.2 µg glycopyrronium, equivalent to 144 µg glycopyrrolate, and 38.4 µg formoterol), were 3.1 (4.7) ms and 7.6 (9.2) ms, respectively, and excluded the clinically relevant threshold of 10 ms. Therefore, single dose administration of GFF MDI and supra-therapeutic doses of glycopyrrolate/formoterol fumarate do not prolong the QT interval. Refer to Table 15 to Table 16 for the different drug exposure levels. In Study PT003010, of the 24 subject enrolled and treated with at least 1 dose of study drug, treatment-emergent AEs reported by Preferred Term that occurred in ≥2 subjects overall included dizziness, headache, and anemia (4 subjects [16.7%] each), injection site pain and dysmenorrhea (3 subjects [12.5%] each), and somnolence (2 subjects [8.3%]). Below is a summary of principal adverse events based on the integrated analysis of Phase II chronic dosing studies: Cardiovascular safety has been evaluated throughout the Phase I/II program. More than 36,000 ECGs have been evaluated with no unexpected findings considering the class of drugs and population under study. Furthermore, a specific cardiovascular safety study, Study PT003003, assessed cardiovascular effects with Holter monitoring. In the Phase III program, one of the pivotal 24-week studies, Study PT003007, included a 24-hour Holter monitoring sub-study, as well as a comprehensive evaluation of ECGs throughout the Phase III program. No clinically relevant findings were observed at the tested doses of GFF MDI 18/9.6 µg BID (i.e., 18 µg glycopyrrolate, equivalent to 14.4 µg glycopyrronium, and 9.6 µg formoterol), GP MDI 18 µg BID (i.e., 18 µg glycopyrrolate, equivalent to 14.4 µg glycopyrronium) and

		FF MDI 9.6 µg BID. The cardiac safety results are described in detail in Section 2.7.3 Summary of Clinical Efficacy. Clinical cardiac safety for all studies are presented in detail in Integrated Summary of Safety Section 4.1.2 (Overall) and 4.1.2.4 (Summary).

Source: Summary of Clinical Pharmacology Studies, Table 11, page 68-80

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/s/

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RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208294 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: Glycopyrrolate and Formoterol fumurate Dosage Form: Inhalation aerosol Strengths: 9mcg/4.8mcg		
Applicant: Pearl Therapeutics Inc. Agent for Applicant (if applicable):		
Date of Application: June 25, 2015 Date of Receipt: June 25, 2015 Date clock started after UN:		
PDUFA Goal Date: April 25,2016	Action Goal Date (if different):	
Filing Date: August 24, 2015	Date of Filing Meeting: August 3, 2015	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication: COPD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): (b) (4) 107739	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☒	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 022571	Cuvposa	**ODE**	07/28/2017

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☐	☒		Language was added to acknowledgement letter. Sponsor has submitted 07/08/2015.

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients*	☒	☐		PeRC meeting has been scheduled for September 30, 2015.

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

If no, request in 74-day letter.				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☒	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT-IRT 07/20/2015
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 12/21/2012 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/02/2014 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 3, 2015

BACKGROUND: On June 25, 2015, Pearl Therapeutics submitted a 505(b)(2) application for glycoyrrolate/formoterol inhalation aerosol with the proposed indication of COPD. The goal date is April 25, 2016.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brandi Wheeler	Y
	CPMS/TL:	Ladan Jafari	Y
Cross-Discipline Team Leader (CDTL)			
Division Director/Deputy	Badrul Chowdhury Lydia Gilbert McClain		Y Y
Office Director/Deputy			
Clinical	Reviewer:	Stacy Chin	Y
	TL:	Tony Durmowicz	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Suresh Doddapaneni	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Anshu Marathe	Y
Biostatistics	Reviewer:	Bob Abugov	Y
	TL:	David Petullo	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Craig Bertha	Y
	RBPM:	Florence Aisida	Y
• Drug Substance	Reviewer:	Ben Stevens	N
• Drug Product	Reviewer:	Art Shaw	N
• Process	Reviewer:	Brian Rogers	N
• Microbiology	Reviewer:	Nutan Mytel	N
• Facility	Reviewer:	Quallyna Porte	N
• Biopharmaceutics	Reviewer:	Peng Duan	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Nyedra Booker	Y
	TL:	Melissa Hulett	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Roberta Szydlo	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Lissa Owens	N
	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	N
	TL:	Janice Pohlman	Y
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Nichelle Rashid		Y
	Julia Pinto		Y
	Kelly Kitchens		Y
	Kassa Ayalew		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	Pearl intends to reference NDA 17558 Robinul (glycopyrrolate) for PK and nonclinical data. The agency agreed that relative BA assessment was not needed because of large exposure margins.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul Chowdhury **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 11/16/2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRANDI E WHEELER
08/10/2015

LADAN JAFARI
08/10/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 208294

Application Type: NDA

Name of Drug/Dosage Form: Glycopyrrolate and formoterol fumurate inhalation aerosol

Applicant: Pearl Therapeutics

Receipt Date: June 25, 2015

Goal Date: April 25, 2016

1. Regulatory History and Applicant's Main Proposals

Pearl Therapeutics submitted an NDA on June 25, 2015 for glycopyrrolate and formoterol fumurate inhalation aerosol with an indication of COPD.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 18, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Sponsor has submitted waiver*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *Lines should be extended over entire width of column*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsection headings are bolded. Additional periods after subsection 13.1.*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRANDI E WHEELER
08/10/2015

LADAN JAFARI
08/10/2015