CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207923Orig1s000

OTHER REVIEW(S)

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:	October 21, 2015
To:	Badrul Chowdhury, MD, PhD, Director **Division of Pulmonary, Allergy and Rheumatology (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:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Roberta Szydlo, RPh, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	SEEBRI NEOHALER (glycopyrrolate inhalation powder)
Dosage Form and Route:	Inhalation Powder
Application Type/Number:	207923
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On December 29, 2014, Novartis submitted, for the Agency's review, a New Drug Application (NDA) 207923, for SEEBRI NEOHALER (glycopyrrolate inhalation powder). SEEBRI NEOHALER (glycopyrrolate inhalation powder) is indicated for the long term maintenance (b) (4) treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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 April 10, 2015 and April 13, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for SEEBRI NEOHALER (glycopyrrolate inhalation powder).

2 MATERIAL REVIEWED

- Draft SEEBRI NEOHALER (glycopyrrolate inhalation powder) PPI and IFU received on December 29, 2014 and received by DMPP on October 8, 2015.
- Draft SEEBRI NEOHALER (glycopyrrolate inhalation powder) PPI and IFU received on December 29, 2014, and received by OPDP on October 8, 2015.
- Draft SEEBRI NEOHALER (glycopyrrolate inhalation powder) Prescribing Information (PI) received on December 29, 2104, revised by the Review Division throughout the review cycle, and received by DMPP on October 8, 2015.
- Draft SEEBRI NEOHALER (glycopyrrolate inhalation powder) Prescribing Information (PI) received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on October 8, 2015.
- ARCAPTA NEOHALER (indacaterol inhalation powder) comparator labeling dated September 26, 2012.
- ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder) comparator labeling dated December 18, 2013.

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. In our review of the PPI and IFU the target reading level is at or below an 8th grade 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 PPI and IFU documents using the Arial font, size 10.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI 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 PPI and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PI and IFU.

Please let us know if you have any questions.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TWANDA D SCALES
10/21/2015

LASHAWN M GRIFFITHS
10/21/2015

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

****Pre-decisional Agency Information****

Memorandum

Date: October 19, 2015

To: Christine Ford, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Deputy Director, Division II, OPDP

Subject: NDA 207923
OPDP labeling comments for SEEBRI™ NEOHALER® (glycopyrrolate) inhalation powder, for oral inhalation use (Seebri Neohaler)

In response to DPARP's consult request dated April 13, 2015, OPDP has reviewed the draft labeling (Package Insert [PI], Instructions for Use (IFU), and Carton/Container Labeling) for Seebri Neohaler.

PI:

OPDP's comments on the PI are provided below and are based on the draft labeling titled "207923 uspi 100615 clean.docx" (attached) that was provided via email from DPARP on October 8, 2015.

IFU:

OPDP's comments on the proposed IFU will be provided under separate cover as a collaborative review between the Division of Medical Policy Programs (DMPP) and OPDP.

Carton/Container Labeling:

OPDP has reviewed the proposed carton and container labeling for Seebri Neohaler submitted by the applicant on December 29, 2014, and located at the following:

- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-15-6mcg-sampleblister-6s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-15-6mcg-samplecarton-12s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-15-6mcg-tradeblister-6s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-15-6mcg-tradecarton-60s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebrineohaler-inhaler-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-placebo-demoblister-6s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-placebo-democarton-6s-xxxxxxx.pdf
- \\cdsesub1\evsprod\nda207923\0000\m1\us\seebri-tray-for-inhaler-xxxxxxx.pdf

We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBERTA T SZYDLO
10/19/2015

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: NDA 207923

Application Type: New NDA

Name of Drug: Seebri Neohaler (glycopyrrolate) inhalation powder (capsules)

Applicant: Novartis

Receipt Date: December 29, 2014

Goal Date: October 29, 2015

1. Regulatory History and Applicant's Main Proposals

Novartis submitted a New Drug Application for long term, twice daily anticholinergic treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The PI also includes Patient Information and Instructions for Use.

Carton and container labeling are included in the submission.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) dated December 29, 2014. 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

No SRPI format deficiencies identified in the review of this PI need to be forwarded to the applicant.

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:

YES 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:

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:

YES 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:

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

Selected Requirements of Prescribing Information

• **Initial U.S. Approval**	Required
• **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

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 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:

N/A 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:

N/A 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:

Selected Requirements of Prescribing Information

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:

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:

N/A 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:

YES 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:

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

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 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:

YES 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: *"The following additional adverse reactions have been identified during worldwide post-approval use of glycopyrrolate, the active ingredient in SEEBRI NEOHALER, at higher than the recommended dose."*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 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/

CHRISTINE H CHUNG
09/17/2015

SANDRA L BARNES
09/17/2015

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 # 207923	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) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: Seebri Neohaler Established/Proper Name: glycopyrrolate Dosage Form: Inhalation Powder Strengths: 15.6 mcg per capsule		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: December 29, 2014 Date of Receipt: Same Date clock started after UN:		
PDUFA/BsUFA Goal Date: 10/29/2015	Action Goal Date (if different):	
Filing Date: 2/27/2015	Date of Filing Meeting: 2/6/2015	
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(s)/Proposed change(s): COPD		
Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)	
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)	

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*): n/a	
List referenced IND Number(s): IND 48655	

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/OMPQ 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

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, OBP Biosimilars RPM*** ***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."***	☒	☐		

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 (including new fixed combinations), new indications, new dosage*	☒	☐		

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

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 : sample & demonstration			
	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.***	☐	☐	☒	
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 (OBP or ONDQA)?	☒	☐	☐	
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)? ***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
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

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

End-of Phase 2 meeting(s)? **Date(s):** 7/15/2008 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9/28/2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** No agreement letter 3/26/2009 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2015

BACKGROUND: New 505(b)(1) application for glycopyrrolate inhalation powder in hard capsules. This memo documents the attendees and filing decisions for NDA 207923.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christine Ford	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Banu Karimi-Shah		Y
Division Director/Deputy	Badrul Chowdhury		Y
Office Director/Deputy			
Clinical	Reviewer:	Erika Torjusen	Y
	TL:	Banu Karimi-Shah	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:	Lei He	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Kiya Hamilton	Y
	TL:	David Petullo	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jane Sohn	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw Martin Haber	Y (phone) Y (phone)
	TL:	Craig Bertha	Y
Biopharmaceutics	Reviewer	Ge (Larry) Bai	N
	TL:	John Duan	N
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review – PQ team	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Linda Ng	Y (phone)
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	Y (phone)
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Lydia Gilbert-McClain Brandi Wheeler		Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• 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:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **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
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**: *Not for sterilization but acceptability of specifications for inhalation product*	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ 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, Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

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

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review:

	• notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	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/

CHRISTINE H CHUNG
09/14/2015

SANDRA L BARNES
09/16/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 10, 2015

TO: Christine Ford, R.Ph., Regulatory Project Manager
Erika Torjusen, M.D., M.H.S., Medical Officer
Banu Karimi-Shah, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy, and
Rheumatology Drug Products (DPARP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Susan D. Thompson, M.D., Team Leader for:
Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207923 & 207930

APPLICANT: Novartis Pharmaceuticals Corporation

DRUGS: NDA 207923 glycopyrrolate [Seebri™ Neohaler®]

NDA 207930 indacaterol [Arcapta® Neohaler®] & glycopyrrolate [Seebri™ Neohaler®] inhalation powder hard capsules

NME: No

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATION: Treatment of patients with chronic obstructive pulmonary disease

CONSULTATION REQUEST DATE (signed):	April 9, 2015
INSPECTION SUMMARY GOAL DATE (original):	September 9, 2015
INSPECTION SUMMARY GOAL DATE (extension):	September 10, 2015
DIVISION ACTION GOAL DATE	October 29, 2015
PDUFA DATE:	October 29, 2015

I. BACKGROUND:

NDA 207923: (glycopyrrolate [Seebri™ Neohaler®])
NVA237 (Glycopyrronium bromide [glycopyrrolate]) inhalation treatment, for patients with COPD, is a synthetic quaternary ammonium compound that acts as a competitive antagonist at muscarinic acetylcholine receptors. This drug, formulated as an inhalation powder hard capsule, is delivered via a Single Dose Dry Powder Inhaler (SDDPI) for patients with COPD.

Two clinical trials submitted in support of the applicant's NDA 207923 were selected for inspection. A single clinical site inspection was requested for Studies A2317 and A2318. The site enrolled large numbers of patients, and the treatment groups had large efficacy differences.

Study CNVA237A2317
Study A2317 was a randomized, multi-center, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of NVA237 (glycopyrrolate) 12.5 µg twice daily (BID) in COPD patients with moderate to severe airflow limitation. The purpose of this study was to provide confirmation of the efficacy and safety of the 12.5 µg BID dose of NVA237 in patients with stable, symptomatic COPD with moderate-severe airflow limitation (level 2 and 3) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 criteria. The primary efficacy endpoint was the measured forced expiratory volume in the first second area under the curve over 12 hours (FEV1 [AUC 0-12h]) at Week 12.

Study CNVA237A2318
Study A2318 was a replicate study to A2317. Study A2318 was a randomized, multi-center, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of NVA237 12.5 µg BID in COPD patients with moderate to severe airflow limitation. The purpose of this study was to provide confirmation of the efficacy and

safety of the 12.5 µg BID dose of NVA237 in patients with stable, symptomatic COPD and moderate-severe airflow limitation (level 2 and 3) according to the GOLD 2011 criteria. The primary objective was to demonstrate superiority of NVA237 12.5 µg BID versus placebo with respect to the standardized area under the curve (AUC) for FEV1 between 0 - 12 h post dosing (FEV1 AUC 0-12h) at Week 12 of treatment in COPD patients with moderate or severe airflow limitation.

NDA 207930: QVA 149 (indacaterol [Arcapta® Neohaler®]) & glycopyrrolate [Seebri™ Neohaler®] inhalation powder hard capsules)

QVA149 is a fixed drug combination product of a long acting β2-agonist (LABA) (Indacaterol maleate – QAB149) and a long acting muscarinic antagonist (LAMA) (glycopyrronium bromide [glycopyrrolate] – NVA237) for the treatment of COPD. The combination product is delivered via the Novartis Single Dose Dry Powder Inhaler (SDDPI).

Two clinical trials submitted in support of the applicant's NDA 207930 were selected for inspection. Two clinical sites were requested for Studies A2336 and A2337. The sites enrolled large numbers of patients, and the treatment groups had large efficacy differences.

Study CQVA149A2336

Study A2336 was a randomized, multi-center, double-blind, placebo and active-controlled, parallel group study. The purpose of the study was to compare the efficacy and safety of QVA149 27.5/12.5 µg BID vs. monotherapy components, QAB149 (indacaterol) 27.5 µg BID and NVA237 (glycopyrrolate) 12.5 µg BID as well as placebo in COPD patients with moderate to severe airflow limitation, to support registration of QVA149 in the U.S. The primary objective was to demonstrate the superiority of QVA149 27.5/12.5 µg BID compared to monotherapy components, QAB149 (indacaterol) 27.5 µg BID and NVA237 (glycopyrrolate) 12.5 µg BID, in terms of standardized FEV1 [AUC 0-12] at Week 12. The primary efficacy endpoint was FEV1 [AUC 0-12] at Week 12.

Study CQVA149A2337

Study A2337 was a replicate study to Study A2236. The purpose of this study was to provide efficacy and safety data in COPD patients with moderate to severe airflow limitation to support registration of QVA149 in the US. The primary objective was to demonstrate the superiority of QVA149 27.5/12.5 µg BID compared to monotherapy components, QAB149 (indacaterol) 27.5 µg BID and NVA237 (glycopyrrolate) 12.5 µg BID, in terms of standardized FEV1 [AUC 0-12] at Week 12. The primary efficacy endpoint was FEV1 [AUC 0-12] at Week 12.

II. RESULTS:

Name of CI Location	Study Site/Protocol/ and Number of Subjects Randomized (n)	Inspection Date	Classification*
James Lawrence Pearle, MD California Research Medical Group, Inc. 301 W. Bastanchury Road Suite 220 Fullerton, CA 92835	NDA 207923 Sites: Site #5013 NVA237A2317 n=23 Site #5071 NVA237A2318 n= 6 NDA 207930 Sites: Site #5080 QVA149A2336 n=12 Site #5033 QVA149A2337 n=28	May 19-June11, 2015	VAI
Leonard Dunn, M.D. Clinical Research of West Florida 2147 NE Coachman Rd. Clearwater, FL 33765	NDA 207930 Sites: Site #5082 QVA149A2336 n=14 Site #5027 QVA149A2337 n=32	July 2-10, 2015	NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.
Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. James L. Pearle, M.D.

Fullerton, CA 92835

a. What was inspected:

NDA 207923:
For Study CNVA237A2317, 44 subjects were screened, and 23 subjects were enrolled and randomized. Twenty two subjects completed the study. An audit of twenty two enrolled subjects' records was conducted.

For Study CNVA237A2318, 15 subjects were screened, and six subjects were enrolled and randomized. Six subjects completed the study. An audit of six enrolled subjects' records was conducted.

NDA 207930:
For Study CQVA149A2336, 16 subjects were screened and 12 subjects were enrolled and randomized. Eleven subjects completed the study. An audit of 11 enrolled subjects' records was conducted.

For Study CQVA149A2337, 57 subjects were screened and 29 were enrolled and randomized. Twenty seven subjects completed the study. An audit of 29 enrolled subjects' records was conducted.

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.

b. General observations/commentary:
The inspection was conducted from May 19 to June 11, 2015.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Raw data was verifiable for the primary efficacy endpoint (FEV1). Isolated minor discrepancies were noted in the numerous FEV1 and FVC data points reported for subjects. These discrepancies were adequately explained by the sponsor in an amendment submitted to the NDA on June 1, 2015, in which the sponsor clarified that NDA data (and data listings provided to the field investigator) reflected the subject's best spirometry efforts, subject to review by a clinical specialist at the centralized spirometry vendor. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for failure to conduct the clinical investigation according to the investigational plan (See selected or relevant examples). Specifically,

1. For Protocol CNVA237A2317, some adverse events, including laboratory and ECG labeled as clinically significant (CS) by the clinical investigator were not recorded in the Adverse Events electronic Case Report Form (e-CRF):

    a. Subject 5013003 had bradycardia noted on April 9, 2013 ECG. This was not recorded in the e-CRF.
    b. Subject 5013013 source data indicated the subject had an AE of cellulitis that was not recorded in the e-CRF
    c. Subject 5013028 had an elevated blood glucose on July 26, 2013 (Visit #206), with repeated abnormal value on August 2, 2013. This was not recorded in the e-CRF.

2. Similarly for Protocol CQVA149A2337, some adverse events were not recorded in the Adverse Events electronic Case Report Form (e-CRF):

   a. Subject 5033031 had an elevated blood glucose level on October 3, 2013, with repeated abnormal results on October 9, 2013 labeled as clinically significant. This was not recorded in the e-CRF. Additionally, a post-dose elevated blood pressure on July 12, 2013 (Visit #201) was not recorded in the e-CRF.
   b. Subject 5033050 had an AE of hematoma that was not recorded in the e-CRF.

OSI Comment:
The items above were considered to be isolated or not clinically significant by DPARP and OSI.

Dr. Pearle adequately responded to the Form FDA 483 (List of Inspectional Observations) in a letter dated June 25, 2015.

c. Assessment of data integrity:
Notwithstanding the above observed violations, data submitted by this clinical site appear acceptable in support of this specific indication.

2. Leonard J. Dunn, M.D.
Clearwater, FL 33765

a. What was inspected:

For Study CQVA149A2336, 20 subjects were screened, and 14 were enrolled and randomized. Twelve subjects completed the study. An audit of 14 enrolled subjects was conducted.

For Study CQVA140A2337, 41 subjects were screened, and 32 were enrolled and randomized. Thirty subjects completed the study. An audit of 32 enrolled subjects was conducted.

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.

b. General observations/commentary:
The inspection was conducted from July 2 to July 10, 2015.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Raw data was verifiable for the primary efficacy endpoint. Data was subject to adjudication by the central spirometry vendor and clinical specialist; however, no changes to raw data reported by this site were requested as a result of this process. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable in support of this specific indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two clinical trials submitted in support of the applicant's NDA 207923 were inspected. A single clinical study site (Dr. James Pearle) was selected for audit, for Studies A2317 and A2318.

Two clinical trials submitted in support of the applicant's NDA 207930 were inspected. Two clinical sites (Dr. James Pearle and Dr. Leonard Dunn) were selected for audit, for Studies A2336 and A2337.

The classification for Dr. Dunn is No Action Indicated (NAI). The classification for Dr. Pearle is Voluntary Action Indicated (VAI). Although regulatory violations were noted at Dr. Pearle's site, they did not have significant impact on assessment of efficacy data or human subject safety. Data as reported by the sponsor for these sites is acceptable for use in support of the requested indication.

Note: Regulatory classifications for the inspections of Drs. Pearle and Dunn are preliminary, based on communications with the field investigator, Form FDA 483 (if issued), and full review of the EIR. Regulatory classification will be finalized once regulatory correspondence is issued to the inspected entity. No changes are anticipated in final classification for these inspections for this NDA.

{See appended electronic signature page}
Anthony Orencia, M.D.
Medical Officer
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.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
09/10/2015

JANICE K POHLMAN
09/10/2015

SUSAN D THOMPSON
09/10/2015

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:	August 20, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 207923
Product Name and Strength:	Seebri Neohaler (Glycopyrrolate) Inhalation Powder 15.6 mcg per capsule
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corp.
Submission Date:	December 29, 2014
OSE RCM #:	2015-89
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

As part of the NDA review process for Seebri Neohaler, DPARP requested that we review the proposed container labels, carton labeling, prescribing information, and instructions for use for areas that may 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

Seebri Neohaler will be a single ingredient product containing Glycopyrrolate. Glycopyrrolate is currently marketed in various dosage forms for other indications (peptic ulcers and in anesthesia as a preoperative antimuscarinic) but not as a capsule for inhalation for the proposed indication of long term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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

DMEPA finds the proposed container labels, carton labeling, prescribing information, and instructions for use acceptable.

4 CONCLUSION

DMEPA concludes that the proposed container labels, carton labeling, prescribing information, and instructions for use are acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Seebri Neohaler that Novartis submitted on December 29, 2014.

Table 2. Relevant Product Information for Seebri Neohaler	
Initial Approval Date	N/A
Active Ingredient	Glycopyrrolate
Indication	long term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Route of Administration	Oral Inhalation
Dosage Form	Capsules for Inhalation
Strength	15.6 mcg
Dose and Frequency	Inhale the contents of one capsule twice daily
How Supplied	Capsules packaged in aluminum blister cards and one Neohaler device
Storage	Store in a dry place at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C)

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 Seebri Neohaler labels and labeling submitted by Novartis on December 29, 2014.

- Container label
- Carton labeling
- Professional Sample Blistercards
- Professional Sample Carton Labeling
- Demonstration Carton Labeling
- Demonstration Blistercards
- Instructions for Use (no image)
- Full Prescribing Information (no image)

G.2 Label and Labeling Images

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LISSA C OWENS
08/23/2015

KENDRA C WORTHY
08/24/2015

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

IND or NDA	207923
Brand Name	Seebri Neohaler
Generic Name	Glycopyrrolate
Sponsor	Novartis
Indication	COPD
Dosage Form	Dry powder inhaler (DPI)
Drug Class	Long-acting muscarinic antagonist (LAMA)
Therapeutic Dosing Regimen	12.5 μg twice (b.i.d) daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD not determined, 400 μg is the maximum tested dose.
Submission Number and Date	001, 12/29/2014
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

This study administered a supratherapeutic dose of 400 μg NVA237. No significant QTc prolongation effect of NVA237 was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean difference between NVA237 and placebo 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 ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, partially-blinded, placebo and positive controlled 3-period cross-over study, 73 subjects received 400μg NVA237, placebo, and 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 NVA 400 µg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
NVA237 400 µg	5 min	2.9	(1.0, 4.8)
Moxifloxacin 400 mg	2	11.3	(9.5, 13.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.8 ms.

The supratherapeutic dose (400 µg) produces mean C_{max} values of 20-fold the mean C_{max} for the therapeutic dose (12.5 µg twice (b.i.d) daily). These concentrations are above those for the predicted worst case scenario (patients with severe renal impairment) and show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected patients with severe renal impairment and end stage renal disease will have 2.2-fold the C_{max} compared to patients with normal renal function. Hepatic impairment may decrease glycopyrronium's clearance as it is mainly eliminated by hepatic metabolism. Although exposure data in patients with hepatic impairment is not available, given the relative difference between the supratherapeutic dose and the therapeutic dose, hepatic impairment is not expected to result in exposures above those observed in this study.

2 PROPOSED LABEL

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

12.2 PHARMACODYNAMICS

(b) (4)

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

12.2. Pharmacodynamics

Cardiac Electrophysiology

The effect of SEEBRI NEOHALER on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled double-blind, single-dose, crossover

thorough QTc study in 73 healthy subjects. At the dose 16-fold the therapeutic daily dose, SEEBRI NEOHALER did not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Glycopyrronium bromide is a synthetic quaternary ammonium, antimuscarinic agent. It has been shown to bind to M1, M2 and M3 muscarinic receptor subtypes.

3.2 MARKET APPROVAL STATUS

Glycopyrronium is not approved for marketing for other indications than COPD. The approved route of administration is i.v and oral. Glycopyrronium was approved in the U.S. in 1961 under the brand name ROBINUL.

3.3 PRECLINICAL INFORMATION

The in vitro effect of indacaterol, glycopyrronium and their combination on the hERG channel current was investigated in HEK293 cells stably transfected with hERG cDNA. The indacaterol (free-base) inhibition of hERG tail current is in excess of 5 μg/ml and hERG channel tail current was not inhibited at a concentration of 1 μg/ml, about 200-fold higher than the highest serum concentration of indacaterol found in a patient at the highest examined and reported dose (2 mg). For glycopyrronium the IC50 in this assay could not be determined as a maximum hERG channel block of 18.3% was observed at the highest tested concentration of 100 μM. For QVA149 the investigation revealed no additive effects on hERG channel current at concentrations of up to 30/300μM indacaterol/glycopyrronium in comparison with the two monotherapy components.

The effects seen in the QVA149 inhalation toxicity studies and the safety pharmacology studies were consistent with the known effects of QAB149 (tachycardia, shortened ECG intervals, ischemic heart damage) and NVA237 (tachycardia, shortened ECG intervals) and relate to the exaggerated pharmacological effects of high dose β2-adrenergic receptor agonists and muscarinic receptor antagonists, respectively. The QVA149 mid and high dose groups in the 14-day and 13-week inhalation dog studies as well as the dose groups in the cardiovascular inhalation safety pharmacology study in telemetered dogs showed additive effects on heart rate in comparison with either of the components alone. Toxicokinetic data for co-administration of QAB149 and NVA237 inhalation toxicology studies showed no apparent pharmacokinetic interaction in rats and dogs.

3.4 PREVIOUS CLINICAL EXPERIENCE

The safety and efficacy of SEEBRI NEOHALER were evaluated in a clinical development program that included 2 dose-ranging trials, 2 efficacy and safety trials of 12 weeks duration (placebo-controlled), and a 52-week long-term safety trial.

The 12-week trials treated 867 subjects that had a clinical diagnosis of COPD.

No evident events identified to be of clinical importance per the ICH E 14 guidelines.

3.5 CLINICAL PHARMACOLOGY

Appendix 6 summarizes the key features of NVA237's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 76377. The sponsor submitted the study report CNVA237A2110 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, partially-blinded, 3- period cross over study to evaluate the effects of single dose NVA237 on the corrected QT interval in healthy volunteers, using moxifloxacin and placebo as positive and negative controls

4.2.2 Protocol Number

CNVA237A2110

4.2.3 Study Dates

Study initiation date: 27-Sep-2011 (first patient screened)
Study completion date: 24-Nov-2011 (last subject last visit)

4.2.4 Objectives

Primary objective:

- To evaluate the effect of a single inhaled dose of 400 µg NVA237 on the QTcF interval in healthy subjects.

Secondary objectives:

- To evaluate the effect of a single inhaled dose of 400 µg NVA237 on QTcB, heart rate, PR and QRS intervals, blood pressure in healthy subjects
- To evaluate the pharmacokinetics of a single inhaled dose of 400 µg NVA237 in healthy subjects
- To evaluate safety and tolerability of a single inhaled dose of 400 µg NVA237 in healthy subjects
- To determine the effect of a single oral dose of moxifloxacin 400 mg on QTcF in healthy subjects to establish assay sensitivity of the study

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, partially-blinded, placebo and positive (moxifloxacin) controlled cross-over study in healthy volunteers. The study consisted of a 20-dayscreening period, three baseline days and three treatment periods, separated by at least 14 day washout

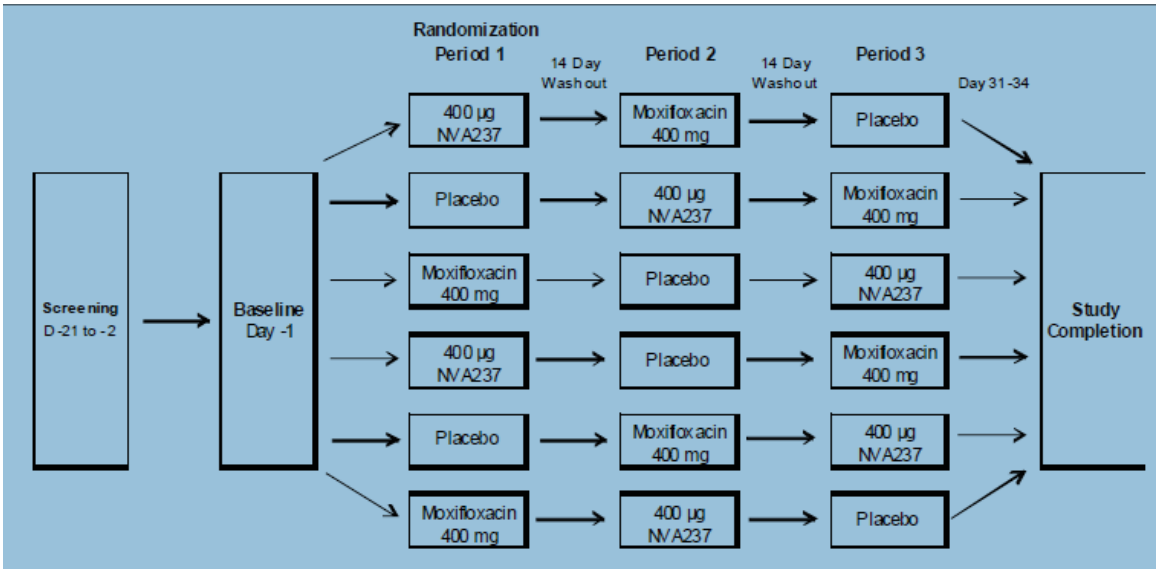
between drug administrations, and followed by a study completion evaluation between 48 hours and 5 days after the last drug administration at the end of study (EOS) visit.

Subjects who met the selection criteria at screening were admitted to the study site at the baseline visit (Day -1) for each period where their eligibility was confirmed and baseline evaluations performed. All baseline safety evaluations were done and the results were available prior to dosing on Day 1.

On baseline days (Day -1), subjects received dinner and a snack, which were part of the meal record, and then started their overnight fast. The meals were standardized for quantity and quality and were provided at approximately the same time for all 3 period baselines.

On Day 1, subjects were randomized to one of the 6 treatment sequences. They received either a single inhaled dose of 400 µg NVA237, its matching placebo given in a double blind fashion or a single oral dose of open-label 400 mg p.o. moxifloxacin. Following dosing, ECG recordings, safety assessments and PK assessments were conducted up to 24 hours post-dose. Lunch, dinner and large snacks were served at about approximately 4, 8 and 12 hours post-dose respectively, and were part of the meal record.

Subjects returned for treatment periods 2 and 3, at a time specified by the investigator for baseline (Baselines 2 and 3), dosing (~ on Days 15 and 29) and follow up assessments up to 24 hours post-dose. All assessments were conducted as in Period 1, at around the same time as in Period 1.



4.2.5.2 Controls

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

4.2.5.3 Blinding

Moxifloxacin was administered open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Study treatments were defined as:

- NVA237 400µg (8 x 50 µg capsules) inhaled via Concept1 device
- NVA237 placebo (8 capsules) inhaled via Concept1 device
- Oral Moxifloxacin 400 mg

Subjects were randomized to one of the following six treatment sequences in the ratio of 1:1:1:1:1:1 such that they received the three treatments in random order.

4.2.6.2 Sponsor's Justification for Doses

Overall the exposure achieved by single dose inhalation of 400 µg NVA237 using the Concept1 device to cover approximately 5 to 6-fold multiple of the steady state PK (AUCtau) exposures in patients with a 50 µg dose of NVA237 (b) (4) . This estimate was based on the fact that the 400 µg NVA237 dose is 8-fold higher than the clinical dose and the steady-state exposures are about 1.3 to 1.4 fold higher than those after a single dose. Therefore, the use of a higher single dose (400 µg) obviated the need for assessing exposure-related effect of multiple dosing. This exposure multiple is in line with the regulatory recommendations for thorough QT studies.

Reviewer's Comment: This reviewer finds the justification for the investigated dose adequate.

4.2.6.3 Instructions with Regard to Meals

Not applicable. Drug is an inhalation product.

4.2.6.4 ECG and PK Assessments

25-hour Holter ECG recordings were used for QT evaluations. These were collected starting 1 hour pre-dose until 24 hours post-dose on dosing days (Day 1 for all three periods).
The time windows that were used for QT analysis in triplicates were: 1 hr pre-dose, 45 min pre-dose, 30 min pre-dose, 15 min pre-dose, pre-dose and post-dose at 5 min, 15 min, 30 min, 60 min, 90 min, and 2, 3, 4, 5, 6, 8, 12 & 24 hr post-dose.
Triplicates were separated by 1 minute intervals.
PK sampling occurred at (pre-dose, 5 min, 15 min, 30, min, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post-dose.

Reviewer's Comment: This reviewer finds the sampling schedule adequate.

4.2.6.5 Baseline

Baseline was defined as the average of the 4 pre-treatment and 1 pre-dose average measurements from the same treatment period.

4.2.7 ECG Collection

25-hour Holter ECG recordings were used for QT evaluations.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 73 patients were randomized with 69 subjects completing the study. The 4 subjects who withdrew did so from different periods resulting in 71 subjects receiving NVA237, 71 receiving moxifloxacin and 71 receiving placebo.

They had an average age of 28 years (range: 18 - 45 years), a mean weight of 74.4 kg (range:54.7 – 108.1 kg) and a mean height of 168 cm (range: 143 – 189 cm). The majority of the subjects were Caucasian (71%).with the population consisting of 52% females.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-averaged period baseline-adjuste mean differences between NVA237 and placebo in QTcF. The sponsor used a mixe model with treatment, period and sequence as fixed effects and subject nested within sequence as a random effect. The result presented in Table 2. NVA237 was concluded not to have a prolongation effect on QTcF as the upper limits of the 2-sided 90% CI for mean differences from placebo did not exceed 10 ms.

Table 2: Sponsor's Result of ΔΔQTcF Interval in NVA237 400 mcg (PD analysis set)

Scheduled time (h)	Estimate of difference	SE	90% CI	P value
0.083	2.97	1.10	1.13, 4.80	0.0090
0.25	-0.32	0.98	-1.95, 1.31	0.7452
0.50	0.17	0.98	-1.47, 1.82	0.8603
1	1.22	0.93	-0.32, 2.75	0.1928
1.5	1.71	0.96	0.11, 3.31	0.0787
2	1.63	1.00	-0.04, 3.29	0.1074
3	0.69	1.01	-1.00, 2.38	0.4977
4	1.07	1.13	-0.81, 2.94	0.3464
5	-2.04	1.44	-4.44, 0.36	0.1608
6	1.14	1.11	-0.72, 3.00	0.3105
8	0.74	1.05	-1.01, 2.49	0.4817
12	-0.14	1.18	-2.10, 1.82	0.9063
24	0.07	1.12	-1.79, 1.94	0.9467

Source: Clinical Study Report, Table 11-3, Page 51/5491

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Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Qur findings are similar to the sponsor's results.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcF effect for moxifloxacin. The analysis result presented in Table 4. The largest lower bound 2-sided 90% is 9.5 ms which was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Table 3: Sponsor's Results of ΔΔQTcF for Moxifloxacin 400 mg (PD analysis set)

Scheduled time (h)	Estimate of difference	SE	90% CI	P-value
0.083	9.02	0.99	7.36, 10.67	<.0001
0.25	0.24	0.81	-1.12, 1.59	0.7728
0.50	5.39	1.12	3.52, 7.25	<.0001
1	10.46	0.99	8.81, 12.10	<.0001
1.5	9.55	1.07	7.77, 11.33	<.0001
2	11.35	1.15	9.45, 13.26	<.0001
3	10.64	1.09	8.82, 12.46	<.0001
4	10.96	1.24	8.88, 13.03	<.0001
5	8.55	1.20	6.54, 10.56	<.0001
6	10.40	1.11	8.56, 12.25	<.0001
8	9.67	1.29	7.52, 11.82	<.0001
12	8.92	1.15	7.00, 10.83	<.0001
24	6.46	1.10	4.62, 8.30	<.0001

Source: Clinical Study Report, Table 11-4, Page 51/5491

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc >450 ms, >480 ms, and >500 ms, and changes from baseline QTc >30 ms and >60 ms. No subject's absolute QTc >450 ms and ΔQTc > 60 ms.

Table 4: Sponsor's Results' Categorical Analysis of QTcF and ΔQTcF

Parameter		QVA149 440/400 µg (N=78) n/m (%)	Moxifloxacin 400mg (N=79) n/m (%)	Placebo (N=79) n/m (%)
QTcF interval (ms)	Increase >30ms	2/78 (2.6%)	0/78 (0)	0/79 (0)
	Increase >60ms	0/78 (0)	0/78 (0)	0/79 (0)
	New >450ms	3/78 (3.8%)	5/78 (6.4%)	0/79 (0)
	New >480ms	0/78 (0)	0/78 (0)	0/79 (0)
	New >500ms	0/78 (0)	0/78 (0)	0/79 (0)
QT interval (ms)	Increase >30ms	1/78 (1.3%)	3/78 (3.8%)	0/79 (0)
	Increase >60ms	0/78 (0)	0/78 (0)	0/79 (0)
	New >450ms	4/76 (5.3%)	6/77 (7.8%)	0/76 (0)
	New >480ms	1/78 (1.3%)	1/78 (1.3%)	0/79 (0)
	New >500ms	0/78 (0)	0/78 (0)	0/79 (0)

n: number of subjects who meet the designated criterion (at least once post-baseline)

- m: Number of subjects at risk for designated change with a non-missing value at both baseline and post-baseline

- N: Total number of subjects who received the treatment in this analysis set

Source: Clinical Study Report, Table 11-6, page 78/11751

4.2.8.3 Safety Analysis

All treatments were well tolerated with no deaths, SAEs or severe adverse events and with only 23% subjects reporting an event at any time during the study. All adverse events were given a CTC grade of 1 or 2 and the majority of events suspected to be related to study drug were reported after subjects received moxifloxacin.

There were no other clinically relevant changes over time observed in clinical laboratory tests, There were no clinically relevant changes in vital signs or in safety 12-Lead ECGs.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 5. C_{max} and AUC values following administration of 400 µg glycopyrronium in the thorough QT study were 20-fold the exposure with inhalations of 12.5 µg b.i.d drug, the intended clinical dose.

Table 5: Summary of PK parameters

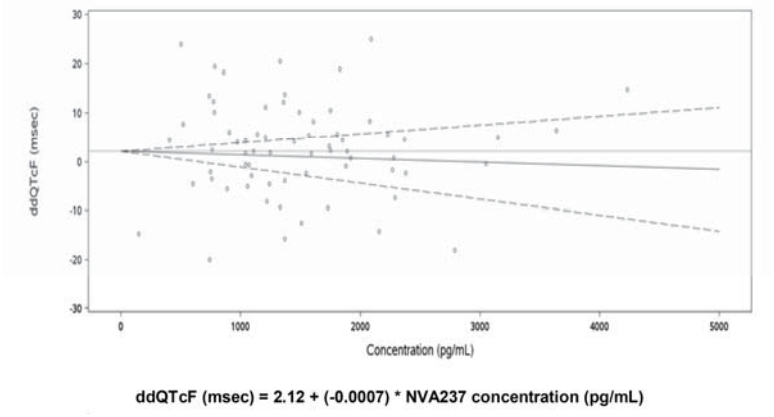
		NVA237 400 ug N=70
Cmax (pg/mL)	Mean	1495
	SD	748.4
	CV%	50.1%
AUClast (h*pg/mL)	Mean	1964
	SD	597.9
	CV%	30.4%
Tmax (h)	Median	0.12
	Range	0.05, 0.28

Source: Applicants report, table 11-7

4.2.8.4.2 Exposure-Response Analysis

The applicant has conducted exposure-response analysis for single and double delta QTcF. Results from the ΔΔQTcF analysis are shown in Figure 1, with no apparent relationship.

Figure 1: Scatter plot showing the relationship between the difference between NVA237 and placebo for change from baseline in QTcF (ddQTcF) at Tmax and NVA237 plasma concentration Cmax (PD analysis set)



Note: The solid regression line describes the linear relationship between the NVA237 plasma concentration and difference to placebo in cardiac parameter change from baseline at Tmax. The dotted lines are the corresponding lower and upper 90% confidence band. The horizontal line is drawn at the estimated intercept.

Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations is presented in Figure 5.

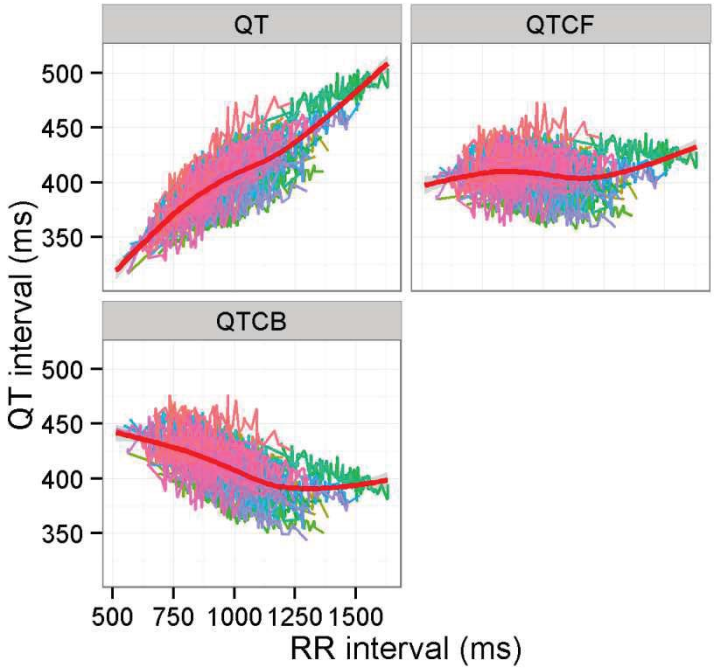
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor only provided QTcF and QTcB correction intervals. This reviewer chose to present QTcF for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcF, and QTcB 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 NVA237 400 mcg

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 6. The largest upper bound of the 2-sided 90% CI for the mean differences between NVA237 400 mcg and placebo is 4.8 ms.

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for NVA237 400 mcg

		Treatment Group			
	Placebo	NVA237 400 MCG			
	ΔQTcF	ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
5 min	-7.4	70	-4.6	2.9	(1.0, 4.8)
15 min	-1.3	70	-1.6	-0.3	(-1.9, 1.3)
30 min	-3.0	70	-2.8	0.2	(-1.7, 2.2)
1	-3.1	70	-1.8	1.2	(-0.5, 2.9)
1.5	-4.0	70	-2.4	1.6	(-0.2, 3.5)
2	-4.2	69	-2.8	1.5	(-0.4, 3.4)
3	-4.0	70	-3.4	0.6	(-1.4, 2.5)
4	-4.7	70	-3.8	0.9	(-1.1, 3.0)
5	-8.0	70	-10.2	-2.2	(-4.6, 0.2)
6	-11.8	70	-10.9	0.9	(-1.1, 3.0)
8	-11.0	71	-10.5	0.5	(-1.6, 2.7)
12	-5.9	69	-6.1	-0.2	(-2.3, 2.0)
24	-6.3	70	-6.2	0.1	(-2.0, 2.1)

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 7. The largest unadjusted 90% lower confidence interval is 9.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.8 ms which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

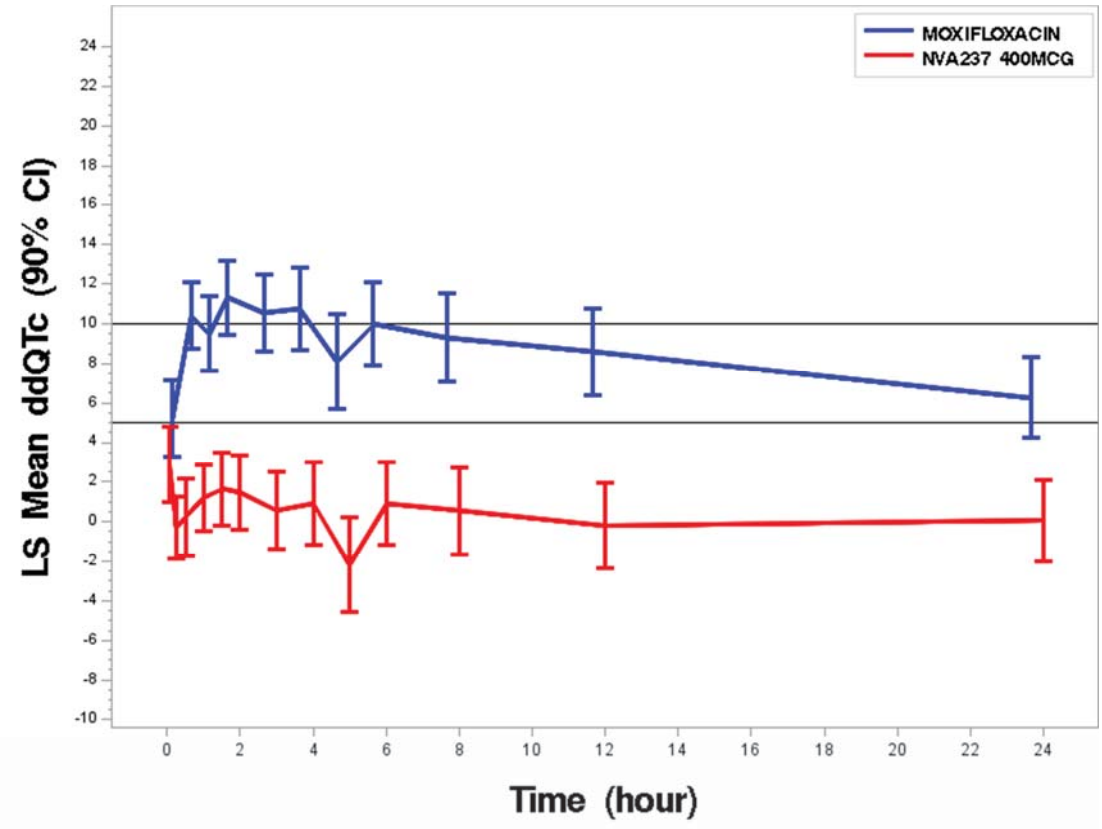
Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin 400 mg

		Treatment Group				
	PLACEBO	MOXIFLOXACIN				
	ΔQTcF	ΔQTcF		ΔΔQTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	90% CI
5 min	-7.4	71	1.4	8.9	(7.0, 10.8)	(6.3, 11.5)
15 min	-1.3	71	-1.2	0.2	(-1.4, 1.7)	(-2.0, 2.3)
30 min	-3.0	71	2.2	5.2	(3.3, 7.1)	(2.6, 7.8)
1	-3.1	71	7.3	10.4	(8.7, 12.1)	(8.1, 12.7)
1.5	-4.0	70	5.5	9.5	(7.6, 11.4)	(6.9, 12.0)
2	-4.2	70	7.1	11.3	(9.5, 13.2)	(8.8, 13.8)
3	-4.0	70	6.5	10.5	(8.6, 12.5)	(7.9, 13.2)
4	-4.7	70	6.0	10.7	(8.7, 12.8)	(7.9, 13.6)
5	-8.0	69	0.1	8.1	(5.7, 10.5)	(4.8, 11.4)
6	-11.8	66	-1.8	10.0	(7.9, 12.1)	(7.1, 12.8)
8	-11.0	66	-1.7	9.3	(7.1, 11.5)	(6.3, 12.3)
12	-5.9	67	2.7	8.6	(6.4, 10.8)	(5.6, 11.5)
24	-6.3	71	-0.0	6.3	(4.2, 8.3)	(3.5, 9.1)

5.2.1.3 Graph of ΔΔQTcF Over Time

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

Figure 3: Mean and 90% CI ΔΔQTcF Time course



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF is above 480 ms.

Table 8: Categorical Analysis for QTcF

	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
Treatment Group					
MOXIFLOXACIN	71	69 (97.2%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
NVA237 400MCG	71	71 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PLACEBO	71	71 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 9 lists the categorical analysis results for ΔQTcF. No subject's change from baseline is above 30 ms.

Table 9: Categorical Analysis of ΔQTcF

	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Treatment Group					
MOXIFLOXACIN	71	71 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NVA237 400MCG	71	71 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PLACEBO	69	69 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bound of the 2-sided 90% CI for the mean differences between NVA237 400 mcg and placebo is 0.4 bpm. Table 11 presents the categorical analysis of HR. No subject who experienced HR greater than 100 bpm was on NVA237 400 mcg.

Table 10: Analysis Results of ΔHR and ΔΔHR for NVA237 400 mcg

		Treatment Group							
		MOXIFLOXACIN				NVA237 400MCG			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	6.7	71	2.7	-4.0	(-5.7, -2.3)	70	5.4	-1.2	(-2.9, 0.4)
15 min	1.4	71	1.8	0.4	(-0.7, 1.6)	70	0.3	-1.2	(-2.3, 0.0)
30 min	0.3	71	2.5	2.1	(1.0, 3.3)	70	-1.8	-2.1	(-3.3, -1.0)
1	-0.6	71	4.3	4.9	(3.6, 6.1)	70	-3.9	-3.3	(-4.6, -2.1)
1.5	-0.9	70	2.9	3.8	(2.7, 5.0)	70	-3.8	-2.9	(-4.0, -1.8)
2	0.1	70	4.0	3.9	(2.6, 5.2)	69	-4.0	-4.1	(-5.4, -2.8)
3	0.7	70	4.0	3.2	(1.8, 4.7)	70	-3.0	-3.7	(-5.2, -2.3)
4	3.4	70	4.6	1.2	(-0.7, 3.1)	70	0.2	-3.2	(-5.1, -1.3)
5	12.8	69	12.4	-0.4	(-2.6, 1.8)	70	6.8	-6.0	(-8.1, -3.8)
6	8.6	66	9.8	1.2	(-0.7, 3.1)	70	4.9	-3.7	(-5.5, -1.8)
8	5.0	66	7.1	2.1	(0.1, 4.0)	71	3.2	-1.8	(-3.8, 0.1)
12	4.9	67	6.6	1.8	(-0.1, 3.7)	69	1.1	-3.7	(-5.6, -1.8)
24	3.0	71	4.1	1.1	(-0.5, 2.7)	70	0.8	-2.2	(-3.8, -0.6)

Table 11: Categorical Analysis of HR

	TOTAL N	HR <= 100 bpm	HR >100 bpm
Treatment Group			
MOXIFLOXACIN	71	68 (95.8%)	3 (4.2%)
NVA237 400MCG	71	71 (100%)	0 (0.0%)
PLACEBO	71	67 (94.4%)	4 (5.6%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bound of the 2-sided 90% CI for the mean differences between NVA237 400 mcg and placebo is 1.7 ms. Table 13 presents the categorical analysis of PR. Two subjects who experienced PR interval greater than 200 ms were on NVA237 400 mcg.

Table 12: Analysis Results of ΔPR and ΔΔPR ΔΔQTcF for NVA237 400 mcg

		Treatment Group							
		MOXIFLOXACIN				NVA237 400MCG			
	ΔPR	ΔPR		ΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	-4.5	71	-1.0	3.5	(1.9, 5.0)	70	-4.3	0.2	(-1.4, 1.7)
15 min	-0.4	71	-0.8	-0.4	(-1.9, 1.0)	70	-2.9	-2.5	(-4.0, -1.0)
30 min	-0.6	71	-0.9	-0.4	(-1.7, 1.0)	70	-2.5	-1.9	(-3.3, -0.6)
1	-0.7	71	-0.2	0.5	(-0.8, 1.9)	70	-4.1	-3.3	(-4.7, -1.9)
1.5	-1.6	70	-1.9	-0.3	(-1.9, 1.3)	70	-5.2	-3.6	(-5.2, -2.0)
2	-1.8	70	-2.2	-0.4	(-2.0, 1.2)	69	-5.4	-3.6	(-5.2, -2.0)
3	-2.0	70	-3.7	-1.7	(-3.3, -0.1)	70	-5.2	-3.2	(-4.8, -1.6)
4	-3.4	70	-5.0	-1.5	(-3.3, 0.2)	70	-7.3	-3.9	(-5.6, -2.2)
5	-6.3	69	-8.1	-1.8	(-3.9, 0.3)	70	-9.7	-3.4	(-5.5, -1.3)
6	-6.9	66	-8.8	-1.9	(-4.0, 0.2)	70	-9.1	-2.2	(-4.2, -0.1)
8	-7.3	66	-8.3	-1.0	(-2.9, 0.9)	71	-9.1	-1.8	(-3.6, 0.1)
12	-4.5	67	-5.8	-1.2	(-3.2, 0.7)	69	-5.6	-1.1	(-3.0, 0.9)
24	-4.3	71	-4.1	0.2	(-1.5, 2.0)	70	-5.2	-0.9	(-2.6, 0.9)

Table 13: Categorical Analysis of PR

	TOTAL N	PR <= 200 ms	PR >200 ms
Treatment Group			
MOXIFLOXACIN	71	69 (97.2%)	2 (2.8%)
NVA237 400MCG	71	69 (97.2%)	2 (2.8%)
PLACEBO	71	67 (94.4%)	4 (5.6%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bound of the 2-sided 90% CI for the mean difference between NVA237 400 mcg and placebo is 1.4 ms. Table 15 presents the categorical analysis of QRS. One subject who experienced QRS interval greater than 110 ms was on NVA237 400 mcg.

Table 14: Analysis Results of ΔQRS and ΔΔQRS ΔΔQTcF for NVA237 400 mcg

		Treatment Group							
		MOXIFLOXACIN				NVA237 400MCG			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
5 min	-0.9	71	0.2	1.1	(0.5, 1.7)	70	-0.6	0.3	(-0.3, 0.9)
15 min	-0.6	71	-0.3	0.2	(-0.4, 0.8)	70	0.0	0.6	(0.0, 1.2)
30 min	-0.1	71	-0.4	-0.4	(-0.9, 0.2)	70	-0.0	0.1	(-0.5, 0.6)
1	0.2	71	-0.1	-0.3	(-0.9, 0.2)	70	0.1	-0.1	(-0.7, 0.4)
1.5	-0.1	70	-0.2	-0.1	(-0.7, 0.5)	70	-0.0	0.1	(-0.5, 0.7)
2	-0.4	70	0.3	0.7	(0.1, 1.3)	69	0.1	0.5	(-0.1, 1.1)
3	-0.5	70	-0.5	0.0	(-0.6, 0.7)	70	-0.4	0.0	(-0.6, 0.7)
4	-0.7	70	-0.6	0.1	(-0.6, 0.8)	70	-0.9	-0.1	(-0.8, 0.6)
5	-0.3	69	-0.4	-0.0	(-0.9, 0.8)	70	0.0	0.3	(-0.5, 1.2)
6	-0.9	66	-1.2	-0.3	(-1.2, 0.5)	70	-0.7	0.1	(-0.7, 1.0)
8	-1.2	66	-1.4	-0.2	(-1.1, 0.6)	71	-1.4	-0.2	(-1.0, 0.6)
12	-0.8	67	-1.1	-0.4	(-1.1, 0.4)	69	-0.1	0.7	(-0.1, 1.4)
24	-0.2	71	-0.6	-0.5	(-1.1, 0.2)	70	-0.2	-0.0	(-0.7, 0.6)

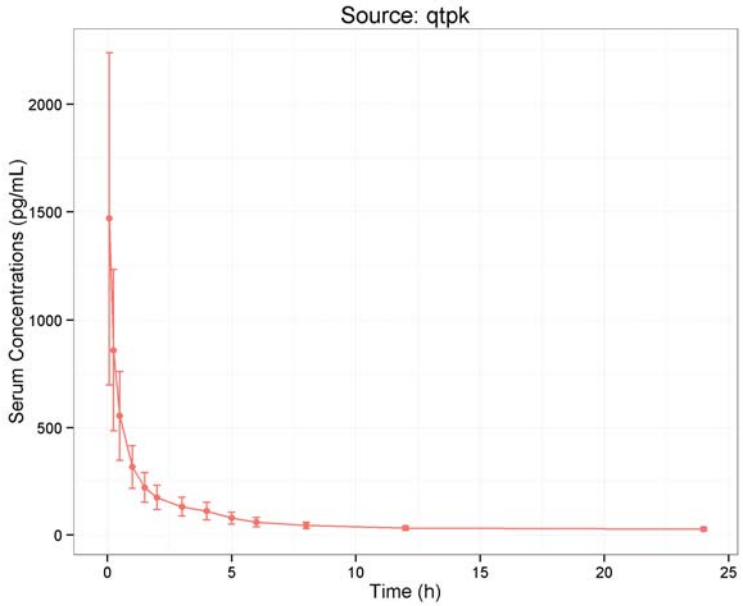
Table 15: Categorical Analysis of QRS

	Total N	QRS <= 110 ms	QRS > 110 ms
Treatment Group			
MOXIFLOXACIN	71	70 (98.6%)	1 (1.4%)
NVA237 400MCG	71	70 (98.6%)	1 (1.4%)
PLACEBO	71	70 (98.6%)	1 (1.4%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 4.

Figure 4: Mean (±SD) glycopyrronium concentration-time profile



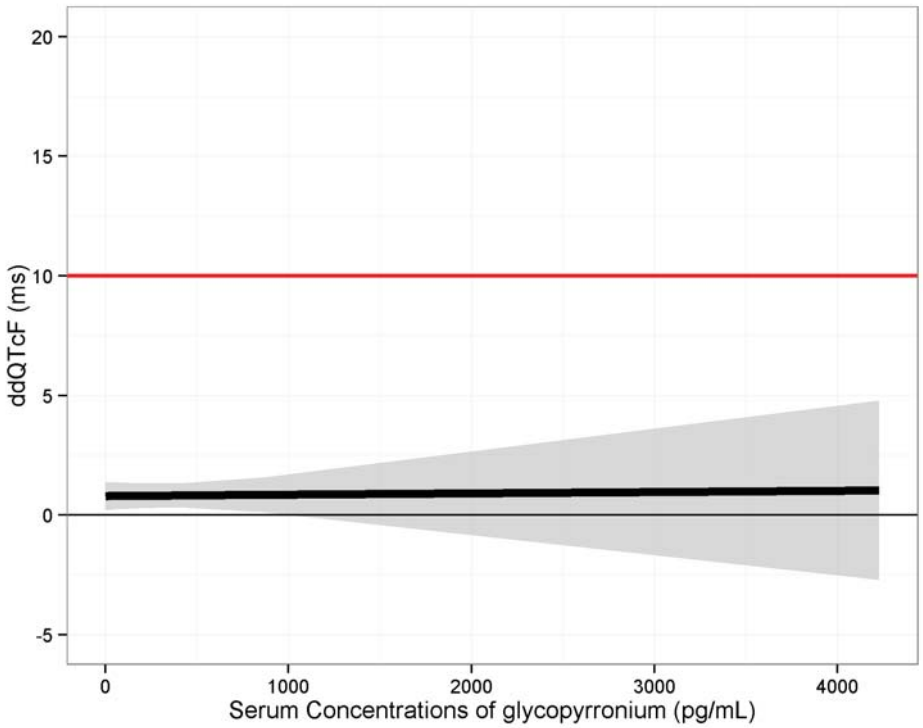
The relationship between ΔQTcF and drug exposure was analyzed using a linear mixed effect model, with the general form:

ΔQTcF = µl + pt + stud+qClkt +Wlk +Clkt + elkt

- µl = treatment specific intercept (active, placebo)
- pt = time specific intercept (as factor)
- q = slope
- Clkt = Concentration for time point t, treatment l, and subject k (subject specific)
- elkt = residual error

A statistically non-significant slope was estimated at 0.0000568 ms*mL/pg with a 95% confidence interval of -0.00107 to 0.00119 ms*mL/pg. Baseline and placebo adjusted QTcF (ΔΔQTcF) was estimated by contrasting placebo effect at concentration zero with the estimate of baseline adjusted QTcF at various concentrations. The relationship between ΔΔQTcF and glycopyrronium concentrations is visualized in Figure 5 with no evident exposure-response relationship.

Figure 5: ΔΔ QTcF vs. glycopyrronium concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 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

No clinically significant effects were seen on PR or QRS intervals.

6 APPENDIX

Highlights of Clinical Pharmacology - NVA237, glycopyrronium bromide

Therapeutic dose	NVA237 12.5 µg twice (b.i.d) daily, inhaled via Concept1 (single dose dry powder inhaler)	
Maximum tolerated dose	Inhaled doses with current NVA237 formulation tested up to 400µg. No MTD determined, all doses tested well tolerated	
Principal adverse events	No dose limiting AEs , most frequent local AE is dry mouth	
Maximum dose tested	Single Dose	400 µg in healthy subjects 200 µg in COPD patients
	Multiple Dose	200 µg, once daily (o.d.) over 4 weeks in COPD patients
Exposures Achieved at Maximum Tested Dose	Single Dose	In healthy subjects (400 µg single dose); Mean (%CV): Cmax: 1495 pg/mL (50%) AUClast: 1964 pg*h/mL (30%) In COPD patients (200 µg single dose); Mean (%CV): Cmax: 565 pg/mL (44%) AUC0-24h: 1028 pg*h/mL (31%)
	Multiple Dose	In COPD patients (200 µg repeated once-daily dosing for 2 weeks); Mean (%CV): Cmax,ss: 865 pg/mL (63%) AUC0-24h,ss: 1780 pg*h/mL (37%)
Range of linear PK	A PopPK analysis concluded that the PK of glycopyrronium following inhalation of NVA237 from 12.5 µg b.i.d. to 50 µg o.d. is linear and dose proportional in COPD patients. In the dose range of 50 µg to 200 µg NVA237, systemic exposure to glycopyrronium as well as total urinary excretion increased about dose -proportionally after single inhalation by healthy volunteers as well as after repeated once-daily inhalation by patients with COPD at pharmacokinetic steady state	
Accumulation at steady state	AUC accumulation ratio, point estimate (90% CI): 100 µg once-daily: 1.44 (1.15-1.79) 200 µg once-daily: 1.69 (1.34-2.13)	
Metabolites	M9, carboxylic acid derivative (direct hydrolysis product of glycopyrronium): no pharmacological activity; Variety of hydroxylated metabolites – activity not tested Glucuronide and/or sulfate conjugates (minor) – activity not tested	
Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of glycopyrronium following NVA237 inhalation with the Concept1 device is estimated to be about 40%. About 90% of systemic exposure to glycopyrronium following inhalation of NVA237 via Concept1 is due to lung absorption and 10% is due to

		gastrointestinal absorption.
	Tmax	Median (range), parent: 0.08 (0.07 – 0.50) h (COPD patients, after single and repeated once-daily dosing) Median (range), M9: 5.0 (3.0 – 8.0) h (healthy volunteers, single dose)
Distribution	Vd/F or Vd	Mean (%CV) Vz/F (after inhalation): 7310 L (20%) Vz (after i.v.): 376 L (21%)
	% bound	38% to 41% (plasma concentration range: 1 to 10 ng/mL)
Elimination	Route	Primary route: Renal excretion of parent (60 to 70% of i.v. dose, up to 20% of inhaled dose). Active tubular secretion contributes to renal elimination. Other routes: Non renal clearance (mainly metabolism, minor contribution of biliary clearance) accounts for about 30 to 40% of systemic clearance.
	Terminal t½	Mean (%CV) 33 (72%) to 57 h (31%) after inhalation, 6.2 h (17%) after i.v. dosing, 2.8 h (65%) after oral dosing
	CL/F or CL	Mean (%CV) CL/F (after inhalation): 99.7 L/h (20%) CL (after i.v.): 42.5 L/h (15%)
Intrinsic Factors	Age	Systemic exposure to glycopyrronium increases with increasing patient age: Compared to a 60 year old subject, average exposure (or AUCtau) was predicted to increase by 37% in an 85 year old subject and to decrease by 18% in a 40 year old subject (based on the PopPK analysis)
	Sex	Gender has no relevant effect on maximal or average glycopyrronium systemic exposure (based on the PopPK analysis)
	Race	The pooled PopPK analysis of NVA237 12.5 µg b.i.d. and 50 µg o.d. showed the absence of any clinically relevant ethnic effect in the Hispanic/Latino and Japanese COPD patients. The analysis of the single dose and steady-state systemic exposure data following inhalation of NVA237 50 µg o.d. did not indicate any clinically relevant ethnic difference across Chinese subjects, COPD Caucasian patients, healthy Caucasian and

		Japanese subjects, and between Chinese and non-Chinese subjects
	Hepatic & Renal Impairment	Renal impairment (RI): Following inhalation, increase of AUClast up to 1.4-fold (on average) in subjects with mild and moderate RI, and up to 2.2-fold in subjects with severe RI and end-stage renal disease, as compared with healthy controls. No effect of RI on Cmax. Using PopPK analysis, the systemic exposure to glycopyrronium following NVA237 12.5 µg b.i.d. dosing was investigated in patients with mild and moderate renal impairment. The simulated median AUCtau for this 12.5 µg b.i.d. regimen in COPD patients with eGFR=30 mL/min/1.73m^2 (i.e. the lower limit of moderate RI) was estimated to be approximately 1.8 fold higher as compared to patients with normal renal function (eGFR=90 mL/min/1.73m^2). Hepatic impairment: Not studied. Since glycopyrronium is predominantly cleared by renal excretion, impairment of hepatic metabolism is not thought to result in a clinically relevant increase of systemic exposure.
Extrinsic Factors	Drug interactions	1) Interaction with cimetidine (single dose of NVA237 given with cimetidine at steady state): Ratio of geometric means of glycopyrronium for coadministration to NVA237 alone: Cmax: 0.94 (90% CI: 0.82-1.07) AUClast: 1.22 (1.12-1.32) CLr: 0.77 (0.70-0.85) 2) Interaction with indacaterol (at steady-state following once daily doses of the free combination and each drug given alone): Ratio of geometric means of glycopyrronium for free combination to NVA237 alone: Cmax: 1.10 (90% CI: 0.93-1.29) AUClast: 1.05 (0.98-1.14) Ratio of geometric means of indacaterol for free combination to indacaterol alone: Cmax: 1.04 (90% CI: 0.94-1.14)

		AUClast: 0.98 (0.92-1.05)
	Food Effects	Not studied. The drug effect is achieved topically in the lungs and food is not expected to affect lung deposition.
Expected High Clinical Exposure Scenario	Systemic effects of high exposures via i.v. route (administered 120 µg glycopyrrolate i.v.) were tested in healthy subjects. In this study a mean Cmax (SD) of 9720 (2230) pg/mL following i.v. administration was achieved that is an approximately 135-fold exposure multiple compared to Cmax,ss following two inhalations of 12.5 µg b.i.d. At these exposure levels there was no trend to tachycardia. Slight bradycardic effects (maximal time matched difference -7 bpm, mean difference over 24 h -2 bpm when compared to placebo), which are typical for low exposures to anticholinergic compounds in young healthy subjects could be observed. No changes in heart rate could be observed after 200 µg NVA237 in COPD patients in the Phase II pilot safety Study NVA237A2206. In the clinical pharmacology studies there were no trends for prolongation of the QT-interval, even at the high exposure levels achieved after intravenous administration of NVA237. These findings were confirmed in a thorough QT-study in which a single inhaled dose of NVA237 400 µg (32 times dose multiple compared to a single dosing unit of 12.5 µg and 16 times the therapeutic daily dose of 25 µg (12.5 µg b.i.d.)) had no clinically relevant effect on the QTcF interval.	

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