

**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: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): **Utibron Neohaler** (indacaterol/glycopyrrolate)

Dosage Form and Route: Inhalation Powder

Application Type/Number: 207930

Applicant: Novartis Pharmaceuticals Corporation

## **1 INTRODUCTION**

On December 29, 2014, Novartis submitted, for the Agency's review, a New Drug Application (NDA) 207930, for QVA149 (indacaterol/glycopyrrolate) inhalation powder. QVA149 (indacaterol/glycopyrrolate) inhalation powder is indicated for the long term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed proprietary name Utibron Neohaler was submitted for review on May 1, 2015 and was deemed conditionally acceptable by the Office of Medication Error Prevention and Risk Management on July 06, 2015.

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 Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder.

## **2 MATERIAL REVIEWED**

- Draft Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder PPI and IFU received on December 29, 2014 and received by DMPP on October 8, 2015.
- Draft Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder PPI and IFU received on December 29, 2014, and received by OPDP on October 8, 2015.
- Draft Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder Prescribing Information (PI) received on December 29, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 8, 2015.
- Draft Utibron Neohaler (indacaterol/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 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of

60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFU the target reading level is at or below an 8<sup>th</sup> 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 MG and IFU documents using the Arial font, size 10.

In our review of the MG and IFU we have:

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

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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

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/s/  
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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 207930  
OPDP labeling comments for UTIBRON NEOHALER<sup>®</sup> (indacaterol  
and glycopyrrolate) inhalation powder, for oral inhalation use  
(Utibron Neohaler)

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

PI:

OPDP's comments on the PI are provided below and are based on the draft labeling titled "207930 uspi 100615 clean.docx" (attached) that was provided via email from DPARP on October 8, 2015.

Medication Guide and IFU:

OPDP's comments on the proposed Medication Guide and 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 Utibron Neohaler submitted by the applicant on December 29, 2014, and located at the following:

- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-27-5-15-6mcg-sampleblister-6s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-27-5-15-6mcg-samplecarton-12s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-27-5-15-6mcg-tradeblister-6s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-27-5-15-6mcg-tradecarton-60s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-27-5-15-6mcg-unitdosecarton-6s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandnameneohaler-inhaler-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-placebo-demoblister-6s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-placebo-democarton-6s-xxxxxxx.pdf](#)
- [\\cdsesub1\evsprod\nda207930\0000\m1\us\brandname-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](mailto:roberta.szydlo@fda.hhs.gov).

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

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/s/  
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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 207930

**Application Type:** New NDA

**Name of Drug:** indacaterol/glycopyrrolate Neohaler inhalation powder

**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 the Medication Guide 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 have been identified in the review of this PI that need to be forwarded to the applicant.

# Selected Requirements of Prescribing Information

## 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

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

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

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

**Comment:**

#### Highlights Limitation Statement

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

**Comment:**

#### Product Title in Highlights

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

**Comment:**

#### Initial U.S. Approval in Highlights

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

**Comment:**

#### Boxed Warning (BW) in Highlights

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

**Comment:**

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

**Comment:**

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

**Comment:**

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

**Comment:**

### Recent Major Changes (RMC) in Highlights

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

**Comment:**

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

**Comment:**

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

**Comment:**

### Indications and Usage in Highlights

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

**Comment:**

### Dosage Forms and Strengths in Highlights

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

**Comment:**

## 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:

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- 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:*

## Selected Requirements of Prescribing Information

### 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.

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

**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:**

## Selected Requirements of Prescribing Information

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

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

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

*Comment:*

#### BOXED WARNING Section in the FPI

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

*Comment:*

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

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

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

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

*Comment:*

- 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.”

## Selected Requirements of Prescribing Information

**Comment:** "The following additional adverse reaction of angioedema has been identified during worldwide post-approval use of indacaterol/glycopyrrolate at higher than the recommended dose."

### 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:**

# Selected Requirements of Prescribing Information

## 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](http://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\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

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

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/  
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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 # 207930	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Utibron Neohaler Established/Proper Name: indacaterol/glycopyrrolate Dosage Form: inhalation powder Strengths: 27.5 mcg indacaterol/15.6 mcg glycopyrrolate 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) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): COPD		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>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)</li> <li>The product is a Qualified Infectious Disease Product (QIDP)</li> <li>A Tropical Disease Priority Review Voucher was submitted</li> <li>A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input checked="" type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): n/a

List referenced IND Number(s): IND 76377, 48649

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

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
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)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>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.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>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)].</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>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.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>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.</i></p>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , # years requested: 3					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes,</b> 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)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>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.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not,</b> explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>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.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>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].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>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)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>  Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>2</sup>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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

<sup>3</sup>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT IRT
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? <b>Date(s):</b> 9/27/11, follow-up 3/7/2012  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 3/19/2014  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> Clinical SPA submitted 2/13/2009, No agreement issued 3/26/2009  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 6, 2015

**BACKGROUND:** New 505(b)(1) application for indacaterol/glycopyrrolate inhalation powder in hard capsules. This memo documents the attendees and filing decisions for NDA 207930.

**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 ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	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) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw Martin Haber	Y (phone) Y (phone)
	TL:	Craig Bertha/Julia Pinto	
Biopharmaceutics	Reviewer:	Sandra Suarez	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		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>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</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>IMMUNOGENICITY (protein/peptide products only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Deficiencies for 74-day letter</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b> <i>Not for sterilization but acceptability of specifications for inhalation product</i></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• 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?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Badrul Chowdhury, Director</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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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.**  
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/s/  
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CHRISTINE H CHUNG  
09/14/2015

SANDRA L BARNES  
09/16/2015

**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 Orenca, 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) (glycopyrrolate) (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:**

<b>Name of CI Location</b>	<b>Study Site/Protocol/ and Number of Subjects Randomized (n)</b>	<b>Inspection Date</b>	<b>Classification*</b>
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,

- I.* 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 Orenca, 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.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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

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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.**  
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/s/  
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ANTHONY J ORENCIA  
09/10/2015

JANICE K POHLMAN  
09/10/2015

SUSAN D THOMPSON  
09/10/2015

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## 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\*\*\***

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<b>Date of This Review:</b>	August 12, 2015
<b>Requesting Office or Division:</b>	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
<b>Application Type and Number:</b>	NDA 207930
<b>Product Name and Strength:</b>	Utibron Neohaler (Indacaterol and Glycopyrrolate) Inhalation Powder, 27.5 mcg/15.6 mcg per capsule
<b>Product Type:</b>	Multi-Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Novartis Pharmaceuticals Corp.
<b>Submission Date:</b>	December 29, 2014
<b>OSE RCM #:</b>	2015-30
<b>DMEPA Primary Reviewer:</b>	Lissa C. Owens, PharmD
<b>DMEPA Team Leader:</b>	Kendra Worthy, PharmD

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## 1 REASON FOR REVIEW

As part of the NDA review process for Utibron 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.

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

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This is a combination product containing Indacaterol and Glycopyrrolate which is not currently marketed. However, Indacaterol is currently marketed as a single ingredient product as Arcapta Neohaler. The Applicant has also submitted an NDA (207923) for a single ingredient Glycopyrrolate product. All of these products have the same dosage form (capsules for inhalation) and utilize the same inhaler (Neohaler) but this proposed combination product and the proposed Glycopyrrolate product will differ in strength and frequency of administration from the marketed Arcapta Neohaler.

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 can be improved to increase the prominence of important information.

#### **4 CONCLUSION & RECOMMENDATIONS**

DMEPA concludes that the proposed container labels, carton labeling, prescribing information, and instructions for use can be improved to increase the prominence of important information.

##### **4.1 RECOMMENDATIONS FOR NOVARTIS**

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

###### **A. All Labels and Labeling**

1. Replace the phrase 'brandname neohaler' with the proposed proprietary name 'Utibron Neohaler'

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

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

<b>Table 2. Relevant Product Information for Utibron Neohaler</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Indacaterol and Glycopyrrolate
<b>Indication</b>	long term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
<b>Route of Administration</b>	Oral Inhalation
<b>Dosage Form</b>	Capsules for Inhalation
<b>Strength</b>	27.5 mcg/15.6 mcg
<b>Dose and Frequency</b>	Inhale the contents of one capsule twice daily
<b>How Supplied</b>	Capsules packaged in aluminum blister cards, one Neohaler device, and a medication guide
<b>Storage</b>	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,<sup>1</sup> along with postmarket medication error data, we reviewed the following Utibron 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

### **G.2 Label and Labeling Images**

(b) (4)



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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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.**  
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/s/  
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LISSA C OWENS  
08/12/2015

KENDRA C WORTHY  
08/12/2015

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

<b>IND or NDA</b>	207930
<b>Brand Name</b>	Utibron Neohaler
<b>Generic Name</b>	Indacaterol, Glycopyrronium
<b>Sponsor</b>	Novartis
<b>Indication</b>	Treatment of COPD
<b>Dosage Form</b>	Dry powder inhaler (DPI)
<b>Drug Class</b>	Fixed dose combinations of a short acting $\beta$ 2-agonist and short acting muscarinic antagonist
<b>Therapeutic Dosing Regimen</b>	indacaterol/glycopyrronium 27.5 /12.5 $\mu$ g twice (b.i.d) daily
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	440/400 $\mu$ g
<b>Submission Number and Date</b>	001 and 12/29/2014
<b>Review Division</b>	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 suprathreshold dose of 440/400  $\mu$ g QVA149. For E14 central tendency analysis, using QTcI, QTcF and QTbtb (QT interval of beat-to-beat) intervals, the largest upper bounds of the 2-sided 90% CI for the mean differences between QVA149 and placebo are 10.1 ms, 10.7 and 10.2 ms, respectively, which exceeded 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  $\Delta\Delta$ QTcI 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, 84 subjects received QVA149 440/400  $\mu$ g, 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 QVA149 440/400 µg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
QVA149 440/400 µg	30 min	8.7	(7.3, 10.1)
Moxifloxacin 400 mg	3	13.0	(11.6, 14.5)
Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
QVA149 440/400 µg	30 min	9.2	(7.6, 10.7)
Moxifloxacin 400 mg	3	13.5	(12.0, 15.0)
Treatment	Time (hour)	$\Delta\Delta QTbtb$ (ms)	90% CI (ms)
QVA149 440/400 µg	30 min	8.3	(6.5, 10.2)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 11.0 ms (QTcI) and 11.5 ms (QTcF).

### Indacaterol

$C_{max}$  and AUC values of indacaterol in this thorough QT study following a single suprathreshold dose of indacaterol 440 µg/400 µg glycopyrronium were 11.7- and 2-fold the therapeutic exposure at indacaterol 27.5/12.5 µg glycopyrronium b.i.d, the intended clinical dose. These concentrations are above those for the predicted worst-case scenario (drug interaction with ketoconazole). It is expected from drug interaction studies that co-administration of indacaterol with ketoconazole can elevate indacaterol's mean  $C_{max}$  as much as 2-fold the  $C_{max}$  of the 27.5 µg dose.

### Glycopyrronium

$C_{max}$  and AUC values of glycopyrronium in the thorough QT study following a single suprathreshold dose of indacaterol 440 µg/400 µg glycopyrronium were 43.75- and 5.85-fold the exposure at indacaterol 27.5/12.5 µg glycopyrronium b.i.d, the intended clinical dose. These concentrations are above those for the predicted worst-case scenario (patients with severe renal impairment). It is expected patients with severe renal impairment and end stage renal disease will have 2.2-fold higher than 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 suprathreshold dose and the therapeutic dose, hepatic impairment is not expected to result in exposures above those observed in this study.

Although, a statistically significant relationship between indacaterol plasma concentration and  $\Delta\Delta QTcI$  has been shown, it seems unlikely that clinically relevant effect is expected at the therapeutic exposure (Figure 5).

## **1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS**

The QTc interval was also studied in TQT studies with each of the monotherapy components.

- No significant QT prolongation effect of indacaterol (150 mcg, 300 mcg and 600 mcg with mean  $C_{max}$  of 1656 pg/mL) was detected in the TQT study, although a shallow but significant relationship between indacaterol plasma concentration and  $\Delta\Delta$  QTcF was observed (under NDA 22383).
- No significant QT prolongation effect glycopyrrolate at the suprathereapeutic dose of 400  $\mu$ g (with mean  $C_{max}$  of 1495 pg/mL) was detected in the TQT study. No evident relationship between glycopyrrolate plasma concentration and  $\Delta\Delta$  QTcF was observed (under NDA 207923).

Although a marginal QT effect of QVA149 was observed at suprathereapeutic exposure more than 9-fold the therapeutic exposure, we consider there will not be a clinically relevant effect at the therapeutic exposure.

## 2 PROPOSED LABEL

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

### 12.2 PHARMACODYNAMICS

(b) (4)

The QTc interval was studied in TQT studies with QVA149 NEOHALER and with each of the monotherapy components. The TQT studies with indacaterol and glycopyrrolate demonstrated that neither of the compounds had a relevant effect on the corrected QT interval at suprathereapeutic and therapeutic doses (for glycopyrrolate only a suprathereapeutic dose was tested).

In a randomized, partially-blinded, placebo- and positive-controlled, crossover TQT study in 84 healthy subjects a suprathereapeutic dose of QVA149 NEOHALER (indacaterol/glycopyrrolate 440/499.2 mcg) was administered. This is a 16/32 dose multiple compared to a single dose of the recommended 27.5/15.6 mcg twice-daily dosage of QVA149 NEOHALER which resulted in exposure multiples for mean  $C_{max}$  of 9.3 for indacaterol and 35.2 for glycopyrrolate compared to steady state pharmacokinetics of QVA149 NEOHALER 27.5/12.5 mcg twice-daily. (b) (4)

The mean maximal change from baseline in QTcI compared to placebo was 8.70 msec (2-sided 90% CI 7.3, 9.83) at 30 minutes after dosing. (b) (4)

(b) (4)

(b) (4)

(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

[REDACTED] The QTc interval was studied in TQT studies with QVA149 NEOHALER and with each of the monotherapy components. The TQT studies with indacaterol and glycopyrrolate demonstrated that neither of the compounds had a relevant effect on the corrected QT interval at suprathreshold and therapeutic doses (for glycopyrrolate only a suprathreshold dose was tested).

In a randomized, partially-blinded, placebo- and positive-controlled, crossover TQT study in 84 healthy subjects a suprathreshold dose of QVA149 NEOHALER (indacaterol/glycopyrrolate 440/499.2 mcg) was administered. This is a 16/32 dose multiple compared to a single dose of the recommended 27.5/15.6 mcg twice-daily dosage of QVA149 NEOHALER which resulted in exposure multiples for mean  $C_{max}$  of 9.3 for indacaterol and 35.2 for glycopyrrolate compared to steady state pharmacokinetics of QVA149 NEOHALER 27.5/12.5 mcg twice-daily. [REDACTED] (b) (4)

[REDACTED] The mean maximal change from baseline in QTcI compared to placebo was 8.70 ms (2-sided 90% CI 7.3, 10.1) at 30 minutes after dosing. Although a marginal QT effect of QVA149 was observed at the suprathreshold dose, it is unlikely there will be a clinically relevant effect at the therapeutic exposure.

[REDACTED] (b) (4)

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

QVA149 NEOHALER contains both indacaterol and glycopyrrolate. These drugs represent 2 different classes of medications (a LABA and an anticholinergic) that have different and additive effects on clinical and physiological indices.

Indacaterol is a long-acting beta2-adrenergic agonist (LABA). When inhaled, indacaterol acts locally in the lung as a bronchodilator. Although beta2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta1-receptors are the predominant receptors in the heart, there are also beta2-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of these receptors is not known, but their presence raises the possibility that even highly selective beta2-adrenergic agonists may have cardiac effects.

Glycopyrrolate is a long-acting muscarinic antagonist (LAMA), which is often referred to as an anticholinergic. 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.

Indacaterol was approved by the European Medicines Agency (EMA) under the trade name Onbrez Breezhaler on November 30, 2009, and by the FDA, under the trade name Arcapta Neohaler, on July 1, 2011

### **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 IC<sub>50</sub> 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 β<sub>2</sub>-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 clinical development program for QVA149 NEOHALER included two (Trial 1 and Trial 2) 12-week, randomized, double-blinded, placebo- and active-controlled, parallel-group trials in subjects with COPD designed to evaluate the efficacy and safety of QVA149 NEOHALER; and one 12-month, randomized, double-blind, active-controlled trial (Trial 3) that evaluated bronchodilation and effects on long-term safety.

The 12-week trials evaluated the efficacy of 2038 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a post-albuterol FEV<sub>1</sub> greater than or equal to 30% and less than 80% of predicted normal values, had a ratio of FEV<sub>1</sub>/FVC of less than 0.7, and were

symptomatic as determined by a Modified Medical Research Council (mMRC) score greater than or equal to 2.

For both single active components of QVA149, thorough QT (TQT) studies have been performed (indacaterol maleate at doses of up to 600 µg o.d. for 14 days and glycopyrronium bromide at a single dose of 400 µg). In addition, a cardiac safety study with QVA149 (CQVA149A2105) had been conducted in healthy volunteers. These studies did not show a consistent potential of QVA149 to prolong QT/QTc duration. QTc prolongation, however, is considered a class-effect of beta-2-adrenoceptor agonists.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of QVA149'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 CQVA149A2109 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, placebo and positive (moxifloxacin) controlled 3-period cross-over study to evaluate the effects of QVA149 on the corrected QT interval in healthy volunteers

#### **4.2.2 Protocol Number**

CQVA149A2109

#### **4.2.3 Study Dates**

Study initiation date: 25-Oct-2013 (first subject first visit)

Study completion date: 22-Dec-2013 (last subject last visit)

#### **4.2.4 Objectives**

##### Primary objective:

- To evaluate the effect of a single inhaled suprathreshold dose of QVA149 (440 µg indacaterol/400 µg glycopyrronium) on the placebo- and baseline-corrected QTcF ( $\Delta\Delta\text{QTcF}$ ) interval in healthy subjects

##### Secondary objectives:

- To evaluate the effect of a single oral dose of moxifloxacin on the placebo-corrected, baseline- adjusted mean QTcF ( $\Delta\Delta\text{QTcF}$ ) change in healthy subjects to confirm assay sensitivity.
- To evaluate the safety and tolerability of a single inhaled dose of QVA149 in healthy subjects

- To evaluate baseline-corrected changes in the ECG parameters (Heart rate (HR); PR interval; QRS duration)

## 4.2.5 Study Description

### 4.2.5.1 Design

A randomized, partially-blinded, placebo and positive (moxifloxacin 400 mg) controlled three period cross-over study to evaluate the effects of QVA149 on the corrected QT interval in healthy male and female subjects, aged between 18 to 45 years (inclusive).

The study consisted of a 20-day Screening period, three baseline days and three treatment periods, separated by at least a 14 day (no longer than approximately 21 days) washout between drug administrations, and followed by a study completion evaluation two to five days after the last drug administration at the end of the study visit.

On Day 1, subjects were randomized in equal numbers to one of the six treatment sequences. The treatment consisted of a single inhaled dose of QVA149, or matching placebo, or a single oral dose of open-label moxifloxacin 400 mg. Following a single dose of study drug, PK assessments, ECG recordings and safety assessments were conducted up to 24 hours post dose.

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

### 4.2.5.2 Controls

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

### 4.2.5.3 Blinding

Moxifloxacin was administered as an open label.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

Study treatments were defined as:

- A: single dose QVA149 440/400 µg (eight capsules of QVA149 containing 55/50 µg indacaterol/glycopyrronium each)
- B: single dose of moxifloxacin 400 mg
- C: single dose of placebo to QVA149 440/400 µg (eight capsules of matching placebo)

Subjects were randomized to one of the following six treatment sequences in the ratio of 1:1:1:1:1:1.

#### 4.2.6.2 Sponsor's Justification for Doses

This study examined sufficient dose multiples for the dose range of QVA149 (55/50 µg o.d. to 27.5/12.5 µg b.i.d) that was investigated in preparation of the US submission of QVA149 during conception of this study. For the upper end of that examined dose range (55/50 µg o.d.) this study with a dose of 440/400 µg would provide data of an 8-fold dose multiple. The 8-fold factor was derived from the maximum potential combined effects of both drug-drug interaction and accumulation on the indacaterol systemic exposure (as those effects are less marked for glycopyrronium). Given the 2-fold indacaterol area under the concentration-time curve (AUC) increase caused by the strong dual inhibitor ketoconazole reflecting the impact of maximal combined inhibition of both P-glycoprotein and CYP3A4 and a mean accumulation ratio of up to 4 (i.e., in the range 2.9 to 3.8) for indacaterol an 8-fold was selected. This exposure multiple was in line with the recommendations for TQT-studies in the ICH E14 guideline. For the 27.5/12.5 µg dose the dose multiple was much higher: 16-fold for indacaterol and 32-fold for glycopyrronium. No active metabolites have been identified for indacaterol and glycopyrronium; therefore the given time-points for ECG extraction were based on the PK of indacaterol and glycopyrronium and considered sufficient for this analysis.

*Reviewer's Comment: Acceptable. QVA149 capsule (27.5 mcg/15.6 mcg) twice-daily is the proposed therapeutic dose. The single dose study provided sufficient exposure that is more than 9-fold the therapeutic exposure with regards to  $C_{max}$ .*

#### 4.2.6.3 Instructions with Regard to Meals

Meals and snacks from Day -1 until after the last PK sample on Day 2 will be standardized with respect to content and quantity for each treatment period.

*Reviewer's Comment: Acceptable; however, food is not believed to alter the exposure of inhaled drugs.*

#### 4.2.6.4 ECG and PK Assessments

##### ECG

Holter extracts for HR and QTc were taken at the following time-points: -60 min, -45 min, -30 min, -15 min, pre-dose, 7 min, 15 min, 30 min, 60 min, 90 min, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 12 h, and 24 h post dose.

##### PK

Pre-dose (0), 0.15, 0.283, 0.53 hour (9, 17, 32 minutes), and 1.03, 1.53, 2.03, 3.03, 4.03, 5.03, 6.03, 8.03, 12.03, and 24.03 hours post-dose.

Post dose PK samples were collected 2 minutes (0.03 h) after the scheduled ECG assessments

*Reviewer's Comment: The sampling scheme is acceptable. However, a 5-min post-dose sample would have been preferred as  $T_{max}$  for glycopyrronium is estimated at 5 min.*

#### 4.2.6.5 Baseline

The sponsor used the average of the -60, -45, -30, -15 and 0 (pre-dose) hour QTc values as baseline.

## 4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

## 4.2.8 Sponsor's Results

### 4.2.8.1 Study Subjects

A total of 84 subjects were enrolled and 73 (86.9%) subjects completed the study. All 84 subjects were included in both the safety analysis set and pharmacodynamic analysis set. Seventy-eight subjects were included in pharmacokinetic analysis set and pharmacokinetic/pharmacodynamic analysis set.

#### 4.2.8.1.1 Primary Analysis

The primary endpoint was time-averaged baseline-adjusted QTcF mean difference between QVA149 and placebo in QTcF. The sponsor used a mixed model with treatment and period as fixed effect and subject as random effect. The QTcF analysis result is presented in Table 2. The upper limit of the 2-sided 90% CI for mean difference between QVA149 and placebo was exceed 10 ms (10.5 ms at 30 minutes after dosing); the threshold for regulatory concern as described in ICH E14 guidelines. The sponsor performed QT beat-to-beat (QTbtb) and QTcI analyses are the results presented in Table 3 and Table 4. The upper limits of the 2-sided 90% CI for mean differences between QVA149 and placebo were below 10 ms (QTbtb was 9.9 ms and QTcI was 9.8 ms).

**Table 2: Sponsor's Result of  $\Delta\Delta$ QTcF Interval in QVA149 440/400 mcg (PD analysis set)**

Parameter	Visit	Scheduled time	Treatment comparison	Estimate difference	SE	90% CI
QTcF interval (ms)	Day 1	0.117 h*	QVA149 vs Placebo	2.95	0.72	(1.75, 4.14)
		0.25 h	QVA149 vs Placebo	8.02	0.62	(6.98, 9.05)
		0.5 h	QVA149 vs Placebo	9.18	0.76	(7.91, 10.46)
		1 h	QVA149 vs Placebo	5.59	0.73	(4.38, 6.79)
		1.5 h	QVA149 vs Placebo	5.16	0.80	(3.84, 6.49)
		2 h	QVA149 vs Placebo	4.01	0.76	(2.74, 5.28)
		3 h	QVA149 vs Placebo	3.93	0.75	(2.68, 5.18)
		4 h	QVA149 vs Placebo	2.64	0.71	(1.46, 3.82)
		5 h	QVA149 vs Placebo	1.92	0.98	(0.30, 3.55)
		6 h	QVA149 vs Placebo	1.90	0.71	(0.71, 3.09)
	8 h	QVA149 vs Placebo	-0.34	0.77	(-1.62, 0.93)	
	12 h	QVA149 vs Placebo	0.58	0.68	(-0.56, 1.71)	
	Day 2	24 h	QVA149 vs Placebo	-0.07	0.67	(-1.19, 1.04)

\*: 0.117 h = 7 minutes

All subjects within the PD population, for whom at least one change from baseline for at least one treatment period were included in the analysis.

The change from baseline was analyzed by a mixed effect model with treatment and period as fixed effects and subject as a random effect.

Source: Clinical Study Report, Table 11-3, page 72/11751

**Table 3: Sponsor’s Result of  $\Delta\Delta$ QTbtb Interval in QVA149 440/400mcg (PD analysis set)**

Parameter	Visit	Scheduled time	Treatment comparison	Estimate difference ( $\Delta\Delta$ QTbtb)	SE	90% CI
QTbtb (ms)	DAY1	0.117 h*	QVA149 vs Placebo	1.03	0.72	(-0.17, 2.24)
		0.25 h	QVA149 vs Placebo	6.70	0.88	(5.24, 8.16)
		0.5 h	QVA149 vs Placebo	8.22	0.98	(6.58, 9.86)
		1 h	QVA149 vs Placebo	5.59	0.83	(4.21, 6.96)
		1.5 h	QVA149 vs Placebo	4.09	0.95	(2.52, 5.67)
		2 h	QVA149 vs Placebo	3.33	0.86	(1.90, 4.75)
		3 h	QVA149 vs Placebo	3.06	0.80	(1.73, 4.39)
		4 h	QVA149 vs Placebo	2.49	0.88	(1.03, 3.95)
		5 h	QVA149 vs Placebo	1.64	0.90	(0.14, 3.13)
	DAY2	6 h	QVA149 vs Placebo	0.44	0.80	(-0.89, 1.78)
		8 h	QVA149 vs Placebo	-1.41	0.74	(-2.64, -0.18)
		12 h	QVA149 vs Placebo	-0.32	0.77	(-1.60, 0.96)
		24 h	QVA149 vs Placebo	-0.92	0.94	(-2.48, 0.64)

\*: 0.117 h = 7 minutes

All subjects within the PD population, for whom at least one change from baseline for at least one treatment period could be calculated, were included in the analysis. Note that subjects who dropped out prior to the Placebo treatment period are not included as the beat-to-beat analysis could not be performed in such case.

The change from baseline was analyzed by a mixed effect model with treatment and period as fixed effects and subject as a random effect.

Source: Clinical Study Report, Table 11-4, page 74/11751

**Table 4: Sponsor’s Result of  $\Delta\Delta$ QTcI Interval in QVA149 440/400 mcg (PD analysis set)**

Parameter	Visit	Scheduled time	Treatment comparison	Estimate of difference	SE	90% CI
QTcI (msec)	DAY1	0.117 hrs	QVA149 vs Placebo	2.76	0.65	(1.67, 3.84)
		0.25 hrs	QVA149 vs Placebo	7.15	0.60	(6.15, 8.15)
		0.5 hrs	QVA149 vs Placebo	8.70	0.68	(7.56, 9.83)
		1 hrs	QVA149 vs Placebo	5.41	0.74	(4.18, 6.64)
		1.5 hrs	QVA149 vs Placebo	5.21	0.80	(3.90, 6.53)
		2 hrs	QVA149 vs Placebo	3.98	0.74	(2.75, 5.21)
		3 hrs	QVA149 vs Placebo	3.84	0.74	(2.61, 5.06)
		4 hrs	QVA149 vs Placebo	2.83	0.69	(1.68, 3.97)
		5 hrs	QVA149 vs Placebo	2.16	0.86	(0.72, 3.60)
		6 hrs	QVA149 vs Placebo	2.01	0.61	(1.00, 3.02)
		8 hrs	QVA149 vs Placebo	-0.48	0.74	(-1.72, 0.76)
		12 hrs	QVA149 vs Placebo	0.40	0.66	(-0.70, 1.50)
	DAY2	24 hrs	QVA149 vs Placebo	-0.14	0.69	(-1.30, 1.01)

Source: Clinical Study Report, Table 11-4, page 207/11751

Reviewer’s Comments: We provided our independent analysis results in Section 5.2.

#### 4.2.8.1.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the  $\Delta$ QTcF effect for moxifloxacin. The analysis results were presented in Table 5. The largest lower bound 1-sided 95% is

12.3 ms which was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

**Table 5: Sponsor’s Results of  $\Delta\Delta$ QTcF for Moxifloxacin 400 mg (PD analysis set)**

Parameter	Visit	Scheduled time	Treatment comparison	Estimate difference	SE	90% CI	P-value	
QTcF interval (ms)	Day 1	0.117 h*	Moxifloxacin vs Placebo	4.25	0.78	(2.95, 5.56)	<.0001	
		0.25 h	Moxifloxacin vs Placebo	-0.51	0.55	(-1.42, 0.40)	0.3535	
		0.5 h	Moxifloxacin vs Placebo	3.54	0.79	(2.23, 4.86)	<.0001	
		1 h	Moxifloxacin vs Placebo	9.98	0.76	(8.71, 11.24)	<.0001	
		1.5 h	Moxifloxacin vs Placebo	10.45	0.66	(9.36, 11.55)	<.0001	
		2 h	Moxifloxacin vs Placebo	11.24	0.62	(10.21, 12.27)	<.0001	
		3 h	Moxifloxacin vs Placebo	13.56	0.77	(12.27, 14.85)	<.0001	
		4 h	Moxifloxacin vs Placebo	12.16	0.61	(11.15, 13.17)	<.0001	
		5 h	Moxifloxacin vs Placebo	8.90	0.83	(7.51, 10.28)	<.0001	
		6 h	Moxifloxacin vs Placebo	8.75	0.65	(7.67, 9.84)	<.0001	
		8 h	Moxifloxacin vs Placebo	8.93	0.74	(7.70, 10.16)	<.0001	
		12 h	Moxifloxacin vs Placebo	8.60	0.66	(7.49, 9.70)	<.0001	
		Day 2	24 h	Moxifloxacin vs Placebo	5.53	0.75	(4.28, 6.78)	<.0001

\*: 0.117 h = 7 minutes

All subjects within the PD population, for whom at least one change from baseline for at least one treatment period may be calculated, were included in the analysis.

The change from baseline was analyzed by a mixed effect model with treatment and period as fixed effects and subject as a random effect.

Source: Clinical Study Report, Table 11-5, page 75/11751

Reviewer’s Comments: We provided our independent analysis results in Section 5.2.

#### 4.2.8.1.3 Categorical Analysis

Table 6 listed 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 >480 ms and  $\Delta$ QTc > 60 ms.

**Table 6: 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

*Reviewer's Comments: We provided our independent analysis results in Section 5.2.*

#### 4.2.8.2 Safety Analysis

- QVA149 440/400 µg and moxifloxacin 400 mg were well tolerated by the subjects in this study with a tolerability profile similar to that of placebo. The most commonly AEs reported in the study were headache, catheter site pain, nausea and feeling hot.
- There were no deaths or SAEs reported in this study. None of the subjects was discontinued for AEs. Most of the AEs were mild and six AEs were moderate in intensity. None of the reported AEs were severe in intensity.

#### 4.2.8.3 Clinical Pharmacology

##### 4.2.8.3.1 Pharmacokinetic Analysis

The PK results for the suprathreshold dose are presented in Table 7. Maximum exposure at steady state ( $C_{max, ss}$ ) following the proposed dosing regimen of 27.5/12.5 µg b.i.d. in COPD patients was estimated at 72.7 (26.1) pg/mL and 30.4 (17.1) pg/mL for Indacaterol and Glycopyrronium, respectively. Following the same regimen, total exposure at steady state ( $AUC_{0-24}$ ) was estimated at 1328 (500) pg.h/mL and 299 (128) pg.h/mL for Indacaterol and Glycopyrronium, respectively.<sup>1</sup>

<sup>1</sup> Summary of Clinical Pharmacology, Table 3-1

### Indacaterol

C<sub>max</sub> and AUC values in the thorough QT study were 11.7- and 2-fold higher following a single suprathereapeutic dose of indacaterol of indacaterol 440 µg/400 µg glycopyrronium suprathereapeutic compared with indacaterol 27.5/12.5 µg glycopyrronium b.i.d, the intended clinical dose.

### Glycopyrronium

C<sub>max</sub> and AUC values in the thorough QT study were 44- and 5.9-fold higher following a single suprathereapeutic dose of indacaterol of indacaterol 440 µg/400 µg glycopyrronium compared with indacaterol 27.5/12.5 µg glycopyrronium b.i.d, the intended clinical dose.

**Table 7: Summary statistics of PK parameters**

Compound: QVA149, Matrix: plasma, Treatment: QVA149 440/400 µg (N=78)

PK parameter (unit)	Analyte	
	QAB149	NVA237
AUC <sub>last</sub> (h*pg/mL)	2730 ± 738 (27.0%) [N=78]	1750 ± 748 (42.9%) [N=78]
C <sub>max</sub> (pg/mL)	854 ± 252 (29.5%) [N=78]	1330 ± 689 (51.9%) [N=78]
T <sub>max</sub> (h) <sup>#</sup>	0.283 (0.267, 0.533) [N=78]	0.150 (0.133, 0.300) [N=78]

Statistics are arithmetic mean ± SD (CV%) [N]  
CV% = Coefficient of variation (%) = sd/arithmetic mean\*100  
# For T<sub>max</sub>, Statistics are median (min, max) [N]

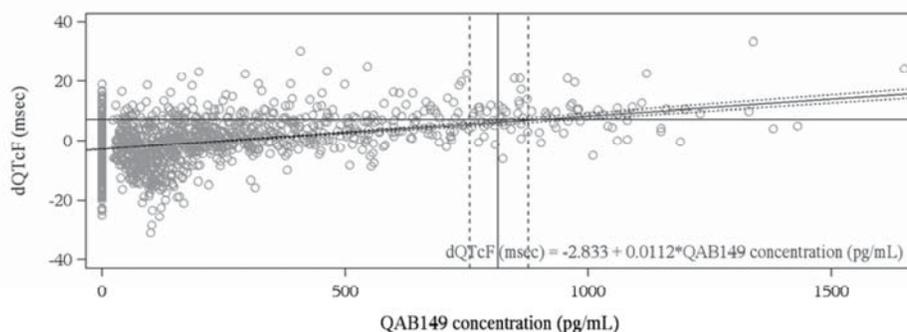
Source: *Applicants report, table 7.*

#### **4.2.8.3.2 Exposure-Response Analysis**

Applicant's exposure response analysis for indacaterol (top panel) and glycopyrronium (bottom panel) is shown in Figure 1.

## Figure 1: Applicant's exposure response analysis

**Figure 11-5 QAB149 plasma concentrations and corresponding change from baseline in QTcF (PK/PD analysis set)**



This graph includes all observations under QVA149 and Placebo. The solid regression line describes a linear relationship between QAB149 plasma concentration (zero concentration for placebo) and cardiac parameter change from baseline.

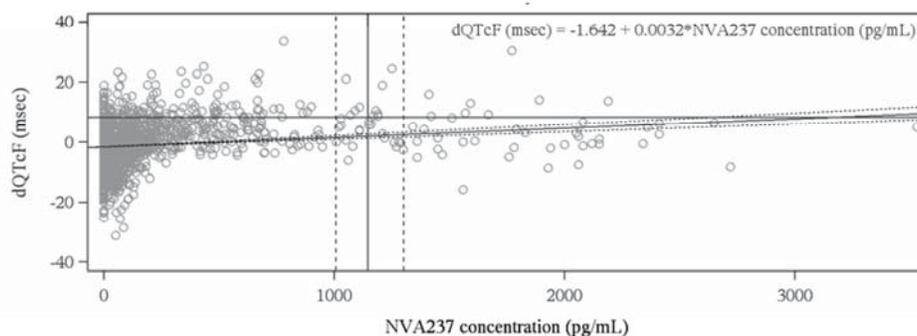
The dotted lines are the corresponding lower and upper 90% confidence band.

The horizontal line is drawn at 10 ms plus the estimated intercept (-2.833).

The vertical lines are the geometric mean and 95% confidence limits for QAB149 Cmax

Source: Applicant's report, Figure 11-5

**Figure 11-6 NVA237 plasma concentrations and corresponding change from baseline in QTcF (PK/PD analysis set)**



This graph includes all observations under QVA149 and Placebo. The solid regression line describes a linear relationship between NVA237 plasma concentration (zero concentration for placebo) and cardiac parameter change from baseline.

The dotted lines are the corresponding lower and upper 90% confidence band.

The horizontal line is drawn at 10 ms plus the estimated intercept (-1.642).

The vertical lines are the geometric mean and 95% confidence limits for NVA237 Cmax.

Source: Applicant's report, Figure 11-6

*Reviewer's Analysis: The reviewer conducted independent analysis. A plot of  $\Delta\Delta QTcI$  vs. drug concentrations is presented in Figure 5.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it appears that QTcI is better than QTcF. The sponsor's

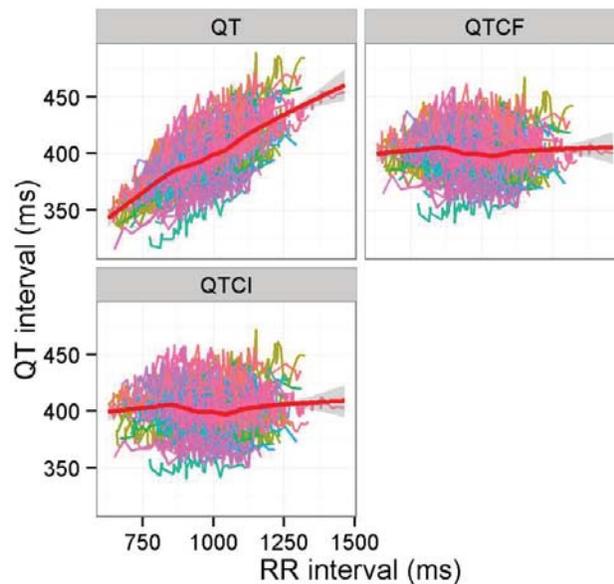
used QTcF as primary endpoint. However, this reviewer used QTcI as primary statistical analysis.

**Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Placebo	79	0.00194	79	0.00153
Moxifloxacin 400 mg	79	0.00264	79	0.00251
QVA149 440/400mcg	78	0.00181	78	0.00189
All	84	0.00143	84	0.00115

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

**Figure 2: QT, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bound of the 2-sided 90% CI for the mean difference between QVA149 440/400 mcg and placebo is 10.1 ms. This reviewer used the same mixed model to analyze QTcF and QTbtb, the largest upper bounds of the 2-sided 90% CI for the mean differences between QVA149 440/400 mcg and placebo are 10.7 ms (see Table 10) and 10.2 ms (see Table 11), respectively. These findings are equal or higher than QTcI values.

**Table 9: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for QVA149 440/400mcg**

Time (h)	QVA149 440/400 mcg				
	$\Delta$ QTcI	$\Delta$ QTcI		$\Delta\Delta$ QTcI	
	LS Mean	N	LS Mean	LS Mean	90% CI
7 min	-2.2	78	0.5	2.7	(1.3, 4.1)
15 min	-1.4	78	5.7	7.1	(6.0, 8.2)
30 min	-1.6	78	7.1	8.7	(7.3, 10.1)
1	-2.0	78	3.4	5.4	(4.0, 6.8)
1.5	-2.1	78	3.2	5.2	(3.9, 6.6)
2	-1.7	78	2.3	4.0	(2.7, 5.3)
3	-2.1	78	1.7	3.8	(2.4, 5.3)
4	-1.5	78	1.3	2.8	(1.4, 4.2)
5	-4.2	78	-2.0	2.2	(0.4, 4.0)
6	-8.9	78	-6.8	2.1	(0.6, 3.6)
8	-9.0	78	-9.4	-0.4	(-2.0, 1.2)
12	0.1	78	0.7	0.6	(-0.9, 2.1)
24	-1.5	78	-1.5	-0.0	(-1.5, 1.4)

**Table 10: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for QVA149 440/400mcg**

	Placebo	QVA149 440/40 mcg			
	$\Delta$ QTcF	$\Delta$ QTcF	$\Delta\Delta$ QTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
0.117	-1.7	78	1.2	2.9	(1.4, 4.4)
0.25	-1.5	78	6.4	7.9	(6.7, 9.1)
0.5	-1.7	78	7.5	9.2	(7.6, 10.7)
1	-2.1	78	3.4	5.6	(4.2, 7.0)
1.5	-2.3	78	2.9	5.2	(3.8, 6.5)
2	-1.9	78	2.1	4.0	(2.7, 5.3)
3	-2.3	78	1.6	3.9	(2.4, 5.4)
4	-1.5	78	1.1	2.6	(1.1, 4.0)
5	-3.8	78	-1.8	2.0	(0.0, 3.9)
6	-8.9	78	-6.8	2.0	(0.3, 3.7)
8	-9.4	78	-9.6	-0.2	(-1.8, 1.4)
12	-0.2	78	0.6	0.8	(-0.7, 2.3)
24	-1.6	78	-1.5	0.1	(-1.4, 1.5)

**Table 11: Analysis Results of  $\Delta$ QTbtb and  $\Delta\Delta$ QTbtb for QVA149 440/400mcg**

	Placebo	QVA149 440/400 mcg			
	$\Delta$ QTbtb	$\Delta$ QTbtb	$\Delta\Delta$ QTbtb		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
7 min	0.8	74	-1.3	1.1	(-0.6, 2.8)
15 min	2.1	74	5.9	7.0	(5.4, 8.5)
30 min	1.5	74	6.6	8.3	(6.5, 10.2)
1	0.7	74	3.0	5.5	(4.0, 7.1)
1.5	1.8	74	2.6	4.0	(2.4, 5.5)
2	1.9	74	1.8	3.1	(1.6, 4.6)
3	1.8	74	1.4	2.8	(1.3, 4.3)
4	2.4	74	1.5	2.3	(0.6, 4.0)
5	0.2	74	-1.4	1.6	(-0.8, 4.0)
6	-4.8	74	-7.5	0.5	(-1.4, 2.4)
8	-5.5	74	-10.1	-1.4	(-3.2, 0.4)
12	4.2	74	0.6	-0.4	(-2.0, 1.3)
24	2.7	74	-1.4	-0.9	(-2.7, 0.8)

### 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 12. The largest unadjusted 90% lower confidence interval is 11.6 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 11.0 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study. The result of largest unadjusted 90% lower confidence intervals of QTcF is 12.0 ms.

**Table 12: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin 400 mg**

		Moxifloxacin 400 mg				
	$\Delta$ QTcI	$\Delta$ QTcI		$\Delta\Delta$ QTcI		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
7 min	-2.2	78	2.7	4.9	(3.6, 6.3)	(3.0, 6.8)
15 min	-1.4	78	-2.1	-0.7	(-1.8, 0.4)	(-2.2, 0.8)
30 min	-1.6	79	1.8	3.4	(2.0, 4.8)	(1.5, 5.3)
1	-2.0	79	7.6	9.6	(8.3, 11.0)	(7.8, 11.5)
1.5	-2.1	79	8.1	10.2	(8.8, 11.5)	(8.3, 12.0)
2	-1.7	79	9.2	10.9	(9.6, 12.2)	(9.2, 12.7)
3	-2.1	78	10.9	13.0	(11.6, 14.5)	(11.0, 15.0)
4	-1.5	78	10.5	12.0	(10.6, 13.4)	(10.0, 14.0)
5	-4.2	78	4.4	8.6	(6.8, 10.4)	(6.1, 11.0)
6	-8.9	78	-0.7	8.2	(6.7, 9.7)	(6.1, 10.3)
8	-9.0	78	-0.6	8.3	(6.8, 9.9)	(6.2, 10.5)
12	0.1	78	8.3	8.3	(6.8, 9.8)	(6.3, 10.3)
24	-1.5	78	3.7	5.2	(3.7, 6.6)	(3.2, 7.1)

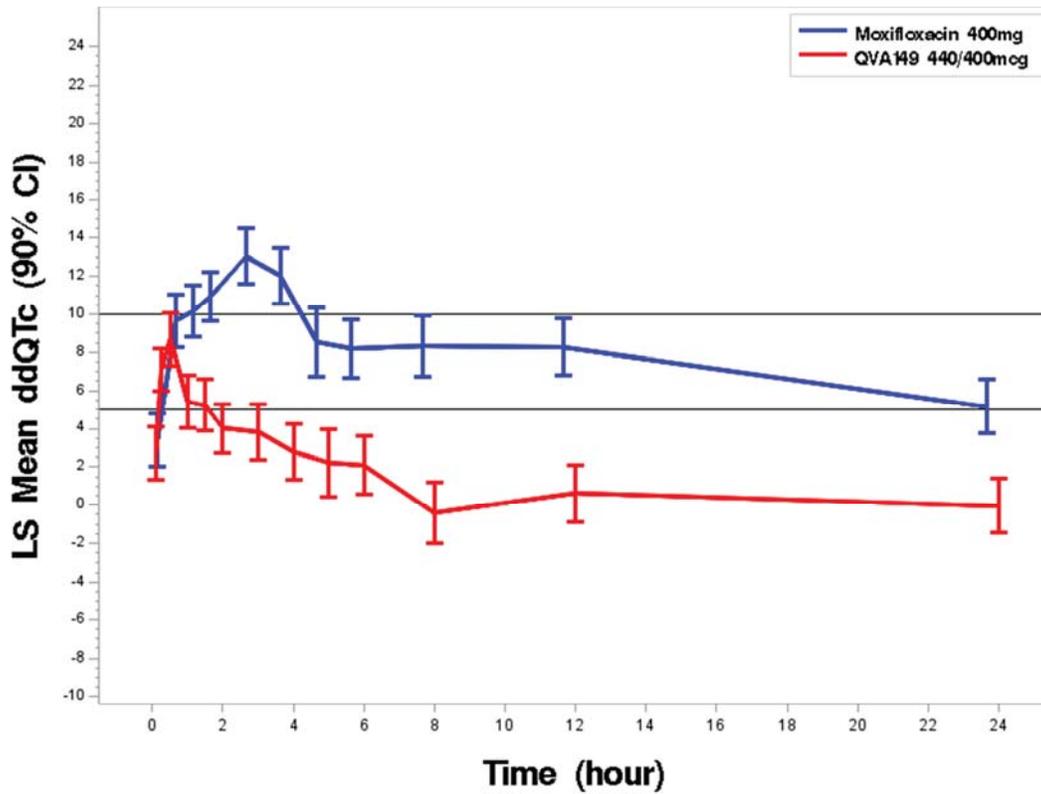
**Table 13: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin 400 mg**

		Moxifloxacin 400 mg				
		$\Delta$ QTcF	$\Delta\Delta$ QTcF			
<b>Time (h)</b>	<b>LS Mean</b>	<b>N</b>	<b>LS Mean</b>	<b>LS Mean</b>	<b>90% CI</b>	<b>Adj. 90% CI</b>
7 min	-1.7	78	2.5	4.2	(2.7, 5.7)	(2.1, 6.3)
15 min	-1.5	78	-2.0	-0.6	(-1.7, 0.6)	(-2.2, 1.1)
30 min	-1.7	79	1.8	3.5	(2.0, 5.0)	(1.4, 5.6)
1	-2.1	79	7.8	10.0	(8.6, 11.3)	(8.1, 11.8)
1.5	-2.3	79	8.1	10.4	(9.0, 11.7)	(8.5, 12.2)
2	-1.9	79	9.3	11.2	(9.9, 12.5)	(9.4, 13.0)
3	-2.3	78	11.2	13.5	(12.0, 15.0)	(11.5, 15.5)
4	-1.5	78	10.6	12.1	(10.6, 13.6)	(10.1, 14.1)
5	-3.8	78	5.2	9.0	(7.1, 11.0)	(6.3, 11.7)
6	-8.9	78	0.1	8.9	(7.2, 10.6)	(6.6, 11.2)
8	-9.4	78	-0.4	9.0	(7.4, 10.6)	(6.8, 11.2)
12	-0.2	78	8.5	8.7	(7.2, 10.2)	(6.7, 10.7)
24	-1.6	78	3.9	5.5	(4.0, 7.0)	(3.5, 7.5)

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups.

**Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcI Timecourse**



**5.2.1.4 Categorical Analysis**

Table 14 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms, between 480 ms and 500, and  $>500$  ms. No subject’s QTcI is above 480 ms.

**Table 14: Categorical Analysis for QTcI**

	Total N	Value $\leq$ 450 ms	450 ms $<$ Value $\leq$ 480 ms	480 ms $<$ Value $\leq$ 500 ms	Value $>$ 500
<b>Treatment Group</b>					
Moxifloxacin 400mg	79	74 (93.7%)	5 (6.3%)	0 (0.0%)	0 (0.0%)
Placebo to QVA149 440/400mcg	79	79 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
QVA149 440/400mcg	78	75 (96.2%)	3 (3.8%)	0 (0.0%)	0 (0.0%)

Table 15 lists the categorical analysis results for  $\Delta$ QTcI. No subject’s change from baseline is above 60 ms.

**Table 15: Categorical Analysis of  $\Delta$ QTcI**

	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
<b>Treatment Group</b>					
Moxifloxacin 400mg	78	78 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo to QVA149 440/400mcg	79	79 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
QVA149 440/400mcg	78	76 (97.4%)	2 (2.6%)	0 (0.0%)	0 (0.0%)

### 5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the  $\Delta$ HR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 16. The largest upper bound of the 2-sided 90% CI for the mean difference between QVA149 440/400 mcg and placebo is 5.9 bpm. Table 17 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in QVA149 440/400 mcg group.

**Table 16: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for QVA149 440/400mcg**

	Treatment Group								
	Placebo	Moxifloxacin 400 mg				QVA149 440/400 mcg			
	Placebo	dQTc		ddQTc		dQTc		ddQTc	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
7 min	5.0	78	2.2	-2.8	(-4.0, -1.6)	78	7.6	2.5	(1.3, 3.8)
15 min	2.1	78	0.9	-1.2	(-2.1, -0.3)	78	7.1	5.0	(4.1, 5.9)
30 min	2.0	79	2.3	0.3	(-0.7, 1.3)	78	4.5	2.6	(1.6, 3.5)
1	0.5	79	2.6	2.1	(1.2, 3.0)	78	0.6	0.0	(-0.9, 1.0)
1.5	-0.3	79	2.3	2.6	(1.7, 3.6)	78	-1.3	-1.0	(-2.0, -0.0)
2	-0.0	79	2.7	2.7	(1.6, 3.9)	78	-0.9	-0.9	(-2.0, 0.3)
3	-0.3	78	2.9	3.2	(2.1, 4.3)	78	-1.2	-0.9	(-2.0, 0.1)
4	0.3	78	3.2	2.9	(1.8, 4.0)	78	-0.8	-1.1	(-2.1, 0.0)
5	7.3	78	8.3	1.0	(-0.4, 2.4)	78	5.7	-1.6	(-3.0, -0.2)
6	7.4	78	9.3	1.9	(0.4, 3.3)	78	5.9	-1.5	(-3.0, -0.1)
8	2.8	78	5.1	2.3	(1.0, 3.6)	78	1.6	-1.2	(-2.5, 0.0)
12	1.5	78	3.6	2.1	(0.8, 3.4)	78	0.4	-1.0	(-2.4, 0.3)
24	1.2	78	2.4	1.3	(0.0, 2.5)	78	0.8	-0.4	(-1.6, 0.9)

**Table 17: Categorical Analysis of HR**

	Total N	HR ≤ 100 bpm	HR >100 bpm
<b>Treatment Group</b>			
Moxifloxacin 400mg	79	79 (100%)	0 (0.0%)
Placebo to QVA149 440/400mcg	79	79 (100%)	0 (0.0%)
QVA149 440/400mcg	78	78 (100%)	0 (0.0%)

**5.2.3 PR Analysis**

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 18. The largest upper bound of the 2-sided 90% CI for the mean difference between QVA149 440/400 mcg and placebo is 1.5 ms. Table 19 presents the categorical analysis of PR. No subject who experienced PR interval greater than 200 ms is in QVA149 440/400 mcg group.

**Table 18: Analysis Results of ΔPR and ΔΔPR for QVA149 440/400mcg**

	Treatment Group								
	Placebo	Moxifloxacin 400mg				QVA149 440/400mcg			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
7 min	-4.5	78	-2.5	2.0	(0.9, 3.2)	78	-6.2	-1.7	(-2.8, -0.6)
15 min	-1.9	78	-1.3	0.6	(-0.6, 1.8)	78	-5.2	-3.3	(-4.5, -2.1)
30 min	-1.7	78	-1.5	0.2	(-1.1, 1.5)	78	-5.5	-3.8	(-5.1, -2.5)
1	-1.4	78	-2.4	-1.0	(-2.1, 0.1)	78	-4.2	-2.8	(-3.9, -1.7)
1.5	-0.8	78	-2.0	-1.2	(-2.6, 0.1)	78	-5.0	-4.2	(-5.6, -2.9)
2	-2.0	78	-2.6	-0.6	(-1.9, 0.8)	78	-3.8	-1.8	(-3.2, -0.5)
3	-2.3	78	-4.5	-2.1	(-3.6, -0.7)	78	-5.2	-2.8	(-4.3, -1.4)
4	-2.7	78	-3.7	-1.0	(-2.4, 0.4)	78	-5.4	-2.7	(-4.1, -1.4)
5	-5.2	78	-6.6	-1.4	(-3.1, 0.3)	78	-6.7	-1.5	(-3.3, 0.2)
6	-8.0	78	-8.7	-0.6	(-2.3, 1.0)	78	-8.4	-0.4	(-2.0, 1.2)
8	-6.9	78	-8.2	-1.3	(-3.0, 0.4)	78	-8.4	-1.5	(-3.2, 0.2)
12	-4.9	78	-5.4	-0.5	(-2.2, 1.2)	78	-5.1	-0.2	(-1.9, 1.5)
24	-3.0	78	-2.4	0.6	(-0.8, 2.1)	78	-3.0	-0.0	(-1.4, 1.4)

**Table 19: Categorical Analysis of PR**

	Total N	PR ≤ 200 ms	PR >200 ms
<b>Treatment Group</b>			
Moxifloxacin 400mg	79	79 (100%)	0 (0.0%)
Placebo to QVA149 440/400mcg	79	79 (100%)	0 (0.0%)
QVA149 440/400mcg	78	78 (100%)	0 (0.0%)

**5.2.4 QRS Analysis**

The statistical reviewer used mixed model to analyze the  $\Delta$  QRS effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 20. The largest upper bound of the 2-sided 90% CI for the mean difference between QVA149 440/400 mcg and placebo is 0.5 ms. Table 21 presents the categorical analysis of QRS. Eleven subjects who experienced QRS interval greater than 110 ms were on QVA149 440/400 mcg.

**Table 20: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for QVA149 440/400 mcg**

	Treatment Group								
	Placebo	Moxifloxacin 400mg				QVA149 440/400mcg			
	$\Delta$ QRS	$\Delta$ QRS	$\Delta\Delta$ QRS		$\Delta$ QRS	$\Delta\Delta$ QRS			
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
7 min	-0.2	78	0.1	0.2	(0.0, 0.5)	78	-0.1	0.1	(-0.1, 0.3)
15 min	0.1	78	-0.1	-0.1	(-0.3, 0.1)	78	0.0	-0.0	(-0.2, 0.2)
30 min	0.0	79	0.2	0.2	(-0.0, 0.4)	78	0.2	0.2	(0.0, 0.4)
1	-0.2	79	0.4	0.6	(0.4, 0.8)	78	0.1	0.3	(0.1, 0.5)
1.5	-0.1	79	0.2	0.3	(0.1, 0.5)	78	-0.1	0.1	(-0.2, 0.3)
2	-0.1	79	0.1	0.2	(0.1, 0.4)	78	-0.1	-0.0	(-0.2, 0.2)
3	0.0	78	0.2	0.2	(-0.1, 0.4)	78	-0.0	-0.0	(-0.3, 0.2)
4	0.0	78	0.2	0.2	(-0.0, 0.4)	78	0.1	0.1	(-0.1, 0.3)
5	0.5	78	0.3	-0.2	(-0.6, 0.2)	78	0.5	0.0	(-0.4, 0.4)
6	-0.3	78	-0.5	-0.2	(-0.6, 0.2)	78	-0.4	-0.1	(-0.5, 0.2)
8	-0.4	78	-0.3	0.1	(-0.2, 0.4)	78	-0.5	-0.1	(-0.5, 0.2)
12	0.4	78	0.6	0.2	(-0.1, 0.5)	78	0.5	0.1	(-0.3, 0.4)
24	-0.0	78	-0.1	-0.1	(-0.4, 0.2)	78	-0.1	-0.1	(-0.4, 0.2)

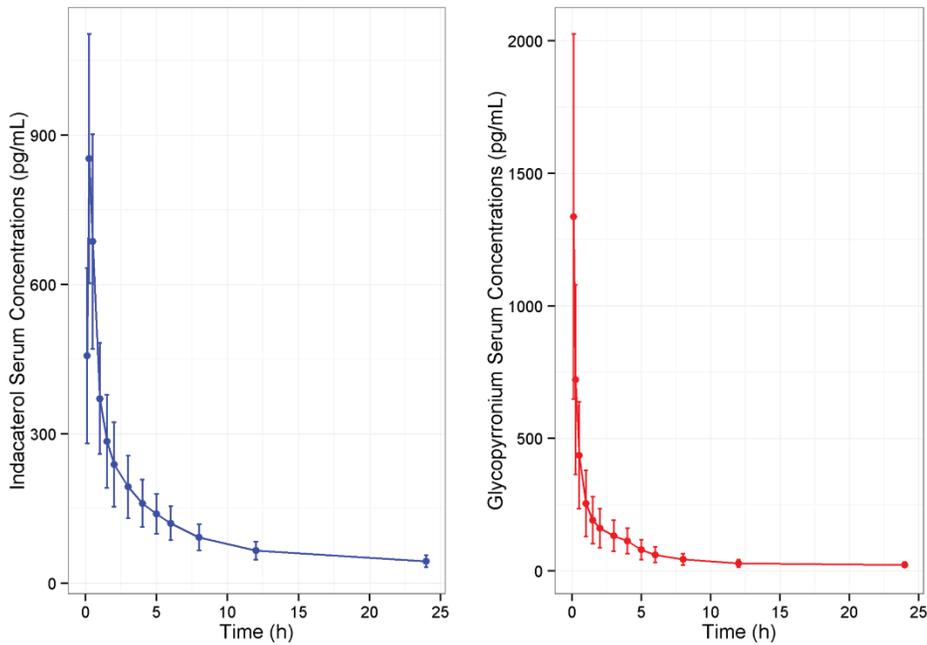
**Table 21: Categorical Analysis of QRS**

	Total N	QRS ≤ 110 ms	QRS > 110 ms
Treatment Group			
Moxifloxacin 400mg	79	65 (82.3%)	14 (17.7%)
Placebo to QVA149 440/400mcg	79	62 (78.5%)	17 (21.5%)
QVA149 440/400mcg	78	67 (85.9%)	11 (14.1%)

**5.3 CLINICAL PHARMACOLOGY ASSESSMENTS**

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

**Figure 4: Mean ±SD plasma concentration-time profiles for Indacaterol (blue line) and Glycopyrronium (red line)**



source: atok

Note: Single dose administration of 440/400 µg indacaterol/glycopyrronium via a dry powder inhaler.

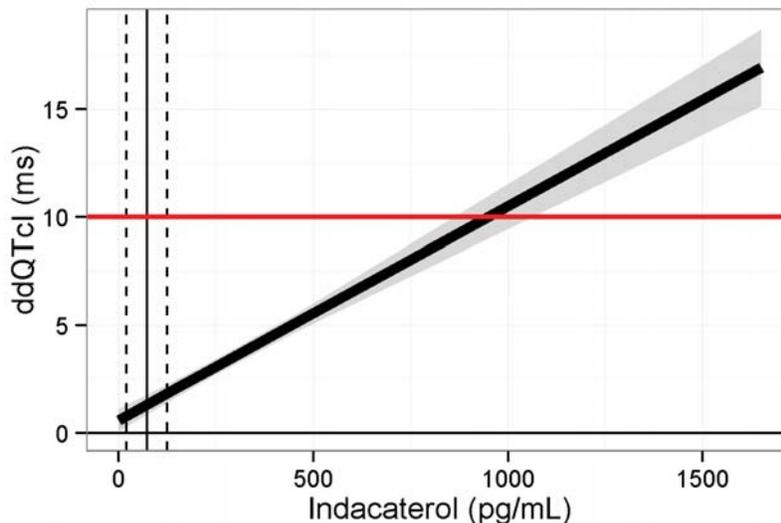
The relationship between  $\Delta QTcI$  and drug exposure was analyzed using a linear mixed effects model, with the general form:

$$\Delta QTcI = \mu_l + p_t + \text{stud} + qCl_{kt} + Wl_k + Cl_{kt} + e_{lkt}$$

- $\mu_l$  = treatment specific intercept (active, placebo)
- $p_t$  = time specific intercept (as factor)
- $q$  = slope
- $Cl_{kt}$  = Concentration for time point  $t$ , treatment  $l$ , and subject  $k$  (subject specific)
- $e_{lkt}$  = residual error

Baseline and placebo adjusted QTcF ( $\Delta\Delta QTcF$ ) was estimated by contrasting placebo effect at concentration zero with the estimate of baseline adjusted QTcF at various concentrations. The relationship between  $\Delta\Delta QTcF$  and indacaterol concentrations is visualized in Figure 5. Although, a statistically significant relationship between indacaterol and  $\Delta\Delta QTcI$  has been shown (the slope of 0.0099 ms\*mL/pg with a 95% confidence interval of 0.00838 to 0.0114 ms\*mL/ng), this reviewer does not think the relationship is clinically significant because the estimated  $\Delta\Delta QTcF$  at therapeutic  $C_{max,ss}$  of 72.7 pg/mL is estimated to be well below the 10 ms threshold (vertical lines in Figure 5). A similar model where both indacaterol and glycopyrronium were included as covariates was deemed inferior and discarded in favor of the current model.

**Figure 5:  $\Delta\Delta QTcI$  vs. Indacaterol concentration**



*Note: The solid black line and the shaded gray area describe the linear relationship between indacaterol concentration and  $\Delta\Delta QTcI$ . The shaded area represents the 90% CI of that relationship. The vertical lines show the mean (2SD) of estimated Indacaterol  $C_{max}$  at steady state following the therapeutic dosing regimen.*

## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

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

### **5.4.2 ECG assessments**

Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

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

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

#### Highlights of QAB149, indacaterol maleate

Therapeutic dose	75 µg, 150 µg, 300 µg once daily: Orally inhaled	
Maximum tolerated dose	In COPD patients a single dose of 3000 µg was associated with moderate and transient increases in pulse rate, systolic blood pressure and QTc interval.	
Principal adverse events	Cough, oropharyngeal pain, nasopharyngitis, nausea and headache	
Maximum dose tested	Single Dose	3000 µg inhaled via SDDPI (Study A2211, Study B2202)
	Multiple Dose	600 µg once daily over 14 days via Concept1
Exposures Achieved at Maximum Tested Dose	Single Dose	In COPD patients the administration of single 3000 µg dose resulted in average peak serum exposure (C <sub>max</sub> ) of 3.39 ng/mL (36 % CV). AUC <sub>inf</sub> was on average 43.18 ng*h/mL (23%CV) and mean AUC <sub>0-24</sub> was 19.12 ng*h/mL (25%CV).
	Multiple Dose	Administration of once daily doses of 600 µg indacaterol to COPD patients via a Concept1 over 14 days resulted in average peak serum concentration of 0.629 ng/mL (23%CV) on the last day of treatment. Average AUC <sub>0-24</sub> on the last day of treatment was 15.1 ng*h/mL (23%CV).
Range of linear PK	<p>In study B2339 indacaterol was dosed over a period of 14 days at dose levels of 150, 300, and 600 µg. C<sub>max</sub> was shown to increase dose-proportionally over the entire dose range on Day 1 and at steady state (Day 14). AUC<sub>0-24h</sub> increased dose-proportionally over the entire dose-range at steady state, and over a dose-multiple of 2.9 at Day 1. Hence both exposure parameters can be considered dose-proportional over the dose range of 150 µg to 300 µg.</p> <p>The data from Study B2356, which compared doses of 150 µg and below, did not indicate any substantial deviation from dose-proportionality in the dose range between 37.5 µg and 150 µg on repeated once-daily dosing via Concept1.</p>	

<p>Accumulation at steady state</p>	<p>Two studies (Study B2339 and Study A2221) provided results after multiple once-daily dosing of healthy subjects with doses between 150 µg and 600 µg for 14 days with serum concentration-time profiles at Day 1 and Day 14 as well as trough level assessments in between. Study B2223 provided results after multiple dosing of asthmatic patients with three different dosing regimens, i.e. 37.5 µg b.i.d., 75 µg q.d. and 150 µg q.o.d, for 15 days.</p> <p>Accumulation factors (Racc; i.e. Day 14/Day 1 or Day 15/Day 1 ratios) for AUC and Cmax were in the range of 2.9 to 3.8 and 1.6 to 2.8, respectively at steady state of once-daily dosing with doses of indacaterol between 75 µg and 600 µg. In Study B2223 systemic accumulation was greatest for the 37.5 µg b.i.d. regimen and lowest for the 150 µg q.o.d. regimen, with AUC accumulation factors of 5.1 and 2.6, respectively.</p> <p>The analysis of trough levels throughout the course of the three studies revealed that steady-state was reached after 12 to 15 days of daily dosing, regardless of the dosing regimen and the population</p>	
<p>Metabolites</p>	<p>After oral administration of radiolabeled indacaterol in the human ADME study unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 h. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, a N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified</p> <p>Hydroxylation leads to metabolites that are equipotent to indacaterol at the beta 2 receptor in-vitro. However as their relative abundance in the systemic circulation is lower than parent indacaterol, and as a therapeutic effect is locally in the lungs, they are not believed to contribute to therapeutic effects. In Study B2339 average peak exposure (Cmax) and total daily exposure (AUC0-24) of hydroxylated metabolites of indacaterol (QAZ033: P26.9 plus P30.3), were 7% and 11%, respectively, of the corresponding indacaterol exposure.</p>	
<p>Absorption</p>	<p>Absolute/Relative Bioavailability</p>	<p>Absolute bioavailability of an inhaled dose was on average 43% to 45%. Relative bioavailability of an oral dose compared to an inhaled dose was 46%. The bioavailability data together suggest that systemic exposure to indacaterol after inhalation is a composite of pulmonary and intestinal absorption.</p>
	<p>Tmax</p>	<ul style="list-style-type: none"> <li>• indacaterol: achieved approximately 15 minutes after single and repeated inhaled doses.</li> <li>• hydroxylated metabolites (Study B2339): 2.08 h (0.25-12.08)</li> </ul>

Distribution	Vd/F or Vd	Apparent volume of distribution (Vz/F) of indacaterol after inhalation was up to 9775 L ( $\pm 90\%$ CV; Study A2105), indicating that indacaterol was extensively distributed when systemically available. After intravenous infusion mean Vz of indacaterol was 2361 L to 2557 L (Study B2106, Study B2103), respectively.
	% bound	The <i>in vitro</i> human serum and plasma protein binding was high, ranging from 94.1 to 95.3 and 95.1 to 96.2% respectively. <i>In vitro</i> protein binding results were consistent with <i>ex-vivo</i> protein binding measurements. Mild-to-moderate hepatic impairment did not alter the protein binding of indacaterol (Study A2307).
Elimination	Route	<ul style="list-style-type: none"> <li>•Biliary elimination of metabolites and/or parent. More than 90% of total radioactivity after an oral radioactive dose recovered in feces of which the majority is parent indacaterol. Exact % of dose not detectable, because of unknown amount of unabsorbed material contributing to total fecal recovery.</li> <li>•Urinary excretion was generally less than 2% of the dose in studies in which urine was collected. Renal clearance of indacaterol was, on average, between 0.46 and 1.2 L/h.</li> <li>•P-gp transport of indacaterol, oxidative metabolism by CYP3A4, possibly followed by glucuronidation, O- and N-glucuronidation by UGT1A1.</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Indacaterol declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 h. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing with once-daily doses between 75 and 600 <math>\mu\text{g}</math> ranged from 40 to 56 hours.</li> <li>• The T<sub>1/2</sub> of the hydroxylated metabolites was not studied (in Study B2339) however its concentration-time profile between 4 and 24 h post-dose declined with similar kinetics to that of indacaterol.</li> </ul>
	CL/F or CL	Serum clearance of indacaterol of 18.8 L/h to 23.3 L/h determined after intravenous infusion (Study B2103; Study B2106)

Intrinsic Factors	Age	Covariate analysis on age did not indicate a need for change in dosage regimen. However, the population PK analysis indicated that within the COPD analysis population the systemic exposure increased with increasing age (41% increase in peak exposure and 23% increase in steady state AUC <sub>0-24h</sub> within the age range of 48 to 78 years).
	Sex	Results of a covariate analysis in population PK on gender indicated that female COPD patients had on average 11% higher peak serum concentrations and 7% greater AUC <sub>0-24h</sub> values than male COPD patients. The difference does not warrant dose adjustments.
	Race	Indacaterol pharmacokinetics shows no difference between Japanese and Caucasian subjects (Study A2215, and Study A2219) and does not show clinically relevant differences amongst COPD patients of different ethnicities. A PK study in Chinese healthy subjects (Study B2101) did not detect relevant changes in systemic exposure after inhalation of indacaterol when compared to similarly designed healthy subject studies in the Caucasian population. From a population PK modeling approach no ethnic factor was identified in the COPD analysis population that would cause major changes in systemic exposure to indacaterol after inhalation via Concept1.
	Hepatic & Renal Impairment	Mild and moderate hepatic impairment does not alter indacaterol pharmacokinetics or protein binding. Study A2307 studied the impact of mild and moderate (Child Pugh 5-6 and 7-9, respectively) hepatic impairment on the pharmacokinetics of single inhaled doses of 600 µg indacaterol delivered via Concept1. The study could not detect any relevant changes in pharmacokinetics or ex-vivo protein binding of indacaterol in subjects with either mild or moderate hepatic impairment when compared to healthy, demographically-matched control subjects. The effect of severe hepatic impairment on indacaterol pharmacokinetics was not studied. Given the evidence that renal clearance plays a very minor role in elimination of indacaterol, a study in subjects with renal impairment was not conducted.

Extrinsic Factors	Drug interactions	<p>Study A2221 studied PK of indacaterol in subjects homozygous for (AT)7 genotype (Gilbert-Syndrome genotype). Average Cmax as well as AUC increased approx. 20 % in the Gilbert-genotype subjects compared to normal controls.</p> <p>Study A2311 investigated the impact of co-administration of ketoconazole a strong inhibitor of CYP3A4 as well as P-gp on indacaterol PK. Cmax of indacaterol increased under ketoconazole treatment 1.4-fold while AUCinf almost doubled. Tmax was shifted to slighter later time (from median 0.25 h versus 0.50 h). Apparent terminal half-life did not significantly differ between the two treatments.</p> <p>Study A2216 investigated the impact of co-administration of verapamil a potent and selective inhibitor of P-gp on the indacaterol PK. Cmax increased by 1.5-fold, AUC0-24h increased 2-fold and AUCinf increased 1.4-fold. Median Tmax was shifted from 0.25 to 1.0 hours post-dose.</p> <p>Study A2220 investigated the impact of co-administration of erythromycin a moderate inhibitor of CYP3A4 on the PK of indacaterol. Cmax increased marginally by 1.2-fold, AUC0-24h increased 1.4-fold and AUCinf increased 1.6-fold.</p> <p>Study B2107 investigated the impact of co-administration of ritonavir a strong inhibitor of CYP3A4 as well as P-gp on the PK of indacaterol. AUC0-24h of indacaterol increased 1.7-fold, AUClast 1.8-fold and AUCinf 1.6-fold. Cmax of indacaterol was similar between treatments and Tmax was shifted from a median of 0.25 h for indacaterol alone to 0.53 h in the presence of ritonavir. Apparent terminal half-life did not significantly differ between the two treatments.</p>
	Food Effects	<p>Since indacaterol is an inhaled drug, a formal food effect study was not conducted. In the PhIII studies of the clinical development program indacaterol was administered as a morning dose regardless of the timing of food intake.</p>

<p>Expected High Clinical Exposure Scenario</p>	<p>Excessive beta-adrenergic stimulation could result in the occurrence or exaggeration of any of the signs and symptoms, e.g., angina, hypertension or hypotension, tachycardia with rates of up to 200 bpm, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, muscle cramps, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, metabolic acidosis and insomnia.</p> <p>The combined evidence from the clinical as well as the nonclinical investigations on DDI potential indicate that potent inhibition of CYP3A4 has the largest effect on the exposure to indacaterol, and lack of activity of UGT1A1 (the second potential metabolic pathway) may have only minor impact. If effects from the ketoconazole study and the UGT1A1 genotype are added, the potentially strongest increase in systemic exposure would be below two-fold for C<sub>max</sub> and approximately 2-fold for AUC.</p> <p>Therefore, the potential supra therapeutic exposure level caused by metabolic drug-interactions is well covered by the exposure level of a doubling of the highest possible therapeutic dose.</p>
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## Highlights of NVA237, glycopyrronium bromide

Therapeutic dose	NVA237 12.5µg twice (b.i.d) daily, inhaled via Concept 1 (single dose dry powder inhaler) under development	
Maximum tolerated dose	Doses up to 6000 µg orally in clinical use, inhaled doses with current formulation tested up to 200µg. 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	200 µg with current inhalation device
	Multiple Dose	200 µg, once daily (o.d.) over 4 weeks
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV), COPD patients (200 µg single dose) Cmax: 565 pg/mL (44%) AUC0-24h: 1028 pg*h/mL (31%)
	Multiple Dose	Mean (%CV), COPD patients (200 µg repeated once-daily dosing for 2 weeks) Cmax: 865 pg/mL (63%) AUC0-24h: 1780 pg*h/mL (37%)
Range of linear PK	Single dose inhalation in healthy volunteers: 50 µg to 200 µg Repeated once-daily inhalation in COPD patients: 50 µg to 200 µg	
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 NVA237: no pharmacological activity; Variety of hydroxylated metabolites – activity not tested Glucuronide and/or sulfate conjugates (minor) – activity not tested	
Absorption	Absolute/Relative Bioavailability	Absolute bioavailability after inhalation via Concept1 estimated to be about 40% (note, value varies depending on method of data analysis due to different disposition kinetics after inhalation and i.v. dosing). About 90% of systemic exposure following inhalation 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

		<p>to 70% of i.v. dose, up to 20% of inhaled dose). Active tubular secretion contributes to renal elimination.</p> <p>Other routes: Non renal clearance (mainly metabolism, minor contribution of biliary clearance) accounts for about 30 to 40% of systemic clearance.</p>
	Terminal t <sub>1/2</sub>	33 to 57 h after inhalation, 6.2 h after i.v. dosing, 2.8 h after oral dosing
	CL/F or CL	<p>Mean (%CV)</p> <p>CL/F (after inhalation): 99.7 L/h (20%)</p> <p>CL (after i.v.): 42.5 L/h (15%)</p>
Intrinsic Factors	Age	Median steady-state AUC <sub>tau</sub> increased by 70% between COPD patients of age 40 to <45 years and 75 to 80 years (based on a population PK analysis after inhalation of NVA237 50 µg o.d., no data for C <sub>max</sub> )
	Sex	Population PK analysis after inhalation of NVA237 50 µg o.d. showed no apparent effect of sex on exposure
	Race	<p>A population PK analysis after inhalation of NVA237 50 µg o.d. showed no difference in the apparent total clearance of NVA237 between Japanese and Caucasian COPD patients and AUC<sub>tau</sub> at steady-state was similar between the two populations. However, peak exposure was higher in Japanese patients, related to a smaller volume of distribution of the central compartment.</p> <p>In a single dose healthy volunteer study, AUC and C<sub>max</sub> were on average 30 to 40% and 80%, respectively, higher in Japanese than in Caucasians. Renal clearance, the dominant elimination pathway, was not different. Differences in this particular study are thought to be due to variation in lung delivery between populations.</p> <p>The comparison of systemic exposure to NVA237 in Chinese subjects versus the non-Chinese population did not indicate clinically relevant ethnic differences.</p>
	Hepatic & Renal Impairment	Renal impairment (RI): Following inhalation, increase of AUC <sub>last</sub> 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

		<p>effect of RI on C<sub>max</sub>.</p> <p>Hepatic impairment: Not studied. Since NVA237 is predominantly cleared by renal excretion, impairment of hepatic metabolism is not thought to result in a clinically relevant increase of systemic exposure.</p>
Extrinsic Factors	Drug interactions	<p>1) Interaction with cimetidine (single dose of NVA237 given with cimetidine at steady state):</p> <p>Ratio of geometric means of NVA237 for coadministration to NVA237 alone:</p> <p>C<sub>max</sub>: 0.94 (90% CI: 0.82-1.07)</p> <p>AUC<sub>last</sub>: 1.22 (1.12-1.32)</p> <p>CL<sub>r</sub>: 0.77 (0.70-0.85)</p> <p>2) Interaction with indacaterol maleate (at steady-state following once daily doses of the free combination and each drug given alone):</p> <p>Ratio of geometric means of NVA237 for free combination to NVA237 alone:</p> <p>C<sub>max</sub>: 1.10 (90% CI: 0.93-1.29)</p> <p>AUC<sub>last</sub>: 1.05 (0.98-1.14)</p> <p>Ratio of geometric means of indacaterol for free combination to indacaterol alone:</p> <p>C<sub>max</sub>: 1.04 (90% CI: 0.94-1.14)</p> <p>AUC<sub>last</sub>: 0.98 (0.92-1.05)</p>
	Food Effects	<p>Not studied. The drug effect is achieved topically in the lungs and food is not expected to have an impact of lung deposition.</p>
Expected High Clinical Exposure Scenario	<p>Systemic effects of high exposures via i.v. route (administered 120 µg glycopyrrolate i.v.) were tested in healthy subjects. Peak concentrations and AUCs after this i.v. dose were about 50-fold and 6-fold, respectively, higher than the C<sub>max</sub> and AUCs at steady state in patients with COPD who received 50 µg once daily (relating to a multiple of 200-fold on C<sub>max</sub> and 12-fold on daily AUC as expected for a b.i.d dose of 12.5 µg). These exposures were well tolerated. Inhaled doses up to 200 µg with the current device and formulation were tested without providing evidence of dose/exposure related tolerability issues in COPD patients and healthy subjects. Further anticholinergic side effects may occur (urinary obstruction, obstipation, glaucoma, tachycardia, arrhythmia, dry mouth).</p>	

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