

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207930Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	207930
Submission Date	12/29/2014
Proposed Brand Name	UTIBRON NEOHALER
Generic Name	Indacaterol/Glycopyrrolate Inhalation Powder
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Sponsor/Authorized Applicant	Novartis
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	Indacaterol 27.5 mcg/Glycopyrrolate 15.6 mcg inhalation powder hard capsule (equivalent to Indacaterol 27.5 mcg/ Glycopyrronium 12.5 mcg)
Indication	COPD
Dosage Regimen	Indacaterol 27.5 mcg/Glycopyrrolate 15.6 mcg (equivalent to Indacaterol 27.5 mcg/ Glycopyrronium 12.5 mcg), BID

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1. Executive Summary

Novartis has submitted NDA 207930 seeking the marketing approval for Indacaterol/ Glycopyrrolate Inhalation Powder (UTIBRON NEOHALER, a fixed-dose combination product of indacaterol and glycopyrrolate) 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 dosing regimen is twice-daily (BID) inhalation of the contents of one UTIBRON capsule, 27.5 mcg indacaterol/15.6 mcg glycopyrrolate (equivalent to 27.5 mcg indacaterol/12.5 mcg glycopyrrolate) using the NEOHALER inhaler. The Sponsor supports NDA207930 submission with 11 clinical pharmacology studies.

The sponsor has also submitted NDA207923 at the same time as this NDA seeking the marketing approval for Glycopyrrolate Inhalation Powder (SEEBRI NEOHALER) for the same indication with 16 clinical pharmacology studies. The proposed dosing regimen is twice-daily (BID) inhalation of the contents of one SEEBRI capsule, 15.6 mcg glycopyrrolate (equivalent to 12.5 mcg glycopyrrolate) using the NEOHALER inhaler. Since glycopyrrolate is one of the individual components of Indacaterol/Glycopyrrolate Inhalation Powder, some studies were used to support both NDA207923 and NDA207930.

To date, several indacaterol and glycopyrrolate drug products have been approved in the United States:

ARCAPTA NEOHALER (Indacaterol Inhalation Powder, Novartis) was approved on 07/01/2011 under NDA022383 for the same indication as proposed for Indacaterol/ Glycopyrrolate Inhalation Powder and Glycopyrrolate Inhalation Powder. The recommended dosage of ARCAPTA NEOHALER is the once-daily (QD) inhalation of the contents of one 75 mcg ARCAPTA capsule using the NEOHALER inhaler.

Glycopyrrolate has been in clinical use for indications other than COPD for over 40 years and has been approved in more than 70 countries. The approved glycopyrrolate drug products in the United States are shown in Table 1.

Table 1. Approved glycopyrrolate drug products in the United States

Product Name	NDA #	Company	Approved Date	Indications
Robinul [®] and Robinul Forte [®] Tablets	012827	SHIONOGI INC	08/11/1961	For use as adjunctive therapy in the treatment of peptic ulcer.
Robinul [®] Injection	017558	(b) (4)	02/06/1975	In Anesthesia: For use as a preoperative antimuscarinic. In Peptic Ulcer: For use in adults as adjunctive therapy for the treatment of peptic ulcer.
Cuvposa [®] Oral Solution	022571	MERZ PHARMS	07/28/2010	Reduce chronic severe drooling in patients aged 3-16 years.

Note that the approved glycopyrrolate generic drug products are not listed.

Please note that glycopyrronium is the quaternary ammonium ion ('active moiety') of glycopyrrolate. 15.6 mcg glycopyrrolate is equivalent to 12.5 mcg glycopyrronium. "QVA149 27.5/12.5 mcg indacaterol/glycopyrronium" will be used throughout this review, which is equivalent to the proposed labelled dose "QVA149 27.5/15.6 mcg indacaterol/glycopyrrolate".

The following are the major findings of the current review:

- 1) Following oral inhalation from QVA149 inhalation via Concept1 device (NEOHALER), both indacaterol and glycopyrronium were rapidly absorbed and reached peak plasma levels (C_{max}) at 15 min and 5 min, respectively.
- 2) There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled indacaterol and inhaled glycopyrronium based on steady-state exposure. Therefore, the relevant findings and/or conclusions for the monotherapies may be extrapolated to QVA149.
- 3) The dose ranging performed in the QVA149 program included full characterization (dose-ranging) of the individual components (NVA237 and QAB149) and was adequate for the Phase 3 dose selection.
 - NVA237 12.5 mcg BID dosing regimen was selected for confirmation in the Phase 3 studies with NVA237 monotherapy and QVA149 combination product in patients with moderate and severe COPD. For further details refer to the Clinical Pharmacology Review of NDA 207923 by Dr. Lei He.
 - In the dose ranging study for QAB149, all 5 QAB149 doses (27.5 mcg BID, 37.5 mcg QD, 55 mcg QD, 75 mcg QD, and 150 mcg QD) showed statistically significant improvements in both primary and secondary endpoints compared to placebo. 27.5 mcg BID was selected as the dosing regimen for QAB149 to combine with NVA237.

The dosing regimen of QVA149 27.5/12.5 mcg BID was selected for confirmation in the pivotal Phase 3 studies in patients with moderate and severe COPD

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 207930 and finds the application acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Indacaterol /Glycopyrrolate Inhalation Powder (QVA149) is a fixed-dose combination (FDC) of a long-acting β_2 -adrenergic agonist (LABA) (indacaterol, QAB149) and a long-

acting muscarinic antagonist (LAMA) (glycopyrronium bromide, glycopyrrolate, NVA237) for oral inhalation to be administered via a single-dose dry powder inhaler (SDDPI) referred to as the Concept1 device (NEOHALER). The recommended dosing regimen is QVA149 27.5/12.5 mcg BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

The Sponsor supports this NDA submission with 11 clinical pharmacology studies. Some studies which were submitted to support NDA 207923 (SEEBRI NEOHALER, Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis) were also used as supportive studies for this NDA submission.

Please note that since there is no PK interaction between indacaterol and glycopyrrolate, the relevant findings and/or conclusions of clinical pharmacology studies for the monotherapies may be extrapolated to QVA149. Only information based on the studies submitted in this NDA was summarized in this section.

Rationale for Dose and Dosing Frequency Selection

The Clinical Pharmacology reviewer concurs with the selection of QVA149 27.5/12.5 mcg BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The dose ranging performed in the QVA149 program was adequate for the Phase 3 dose selection.

The QVA149 development program includes full characterization (dose-ranging) of the individual components (NVA237 and QAB149) to establish the appropriate dose for each component before proceeding to the QVA149 Phase 3 studies.

- NVA237 12.5 mcg BID dosing regimen was selected for confirmation in the Phase 3 studies with NVA237 monotherapy and QVA149 combination product in patients with moderate and severe COPD. For further details refer to the Clinical Pharmacology Review of NDA 207923 by Dr. Lei He.
- In the dose ranging study for QAB149, all 5 QAB149 doses (27.5 mcg BID, 37.5 mcg QD, 55 mcg QD, 75 mcg QD, and 150 mcg QD) showed statistically significant improvements in both primary and secondary endpoints vs. placebo (Table 2 and Figure 1). 27.5 mcg BID was selected as the dosing regimen for QAB149 to combine with NVA237.

The dosing regimen of QVA149 27.5/12.5 mcg BID was selected for confirmation in the pivotal Phase 3 studies in patients with moderate and severe COPD comparing monotherapies QAB149 27.5 mcg BID, NVA237 12.5 mcg BID, and QAB 75 mcg QD (Figure 2 and Figure 3). Refer to the Clinical Review for further details.

Table 2. Change from period baseline in FEV1 (L) AUC(0-24h) - Study QVA149A2210

Treatment	n	FEV ₁ AUC (L) Baseline Raw Means	Change from BL in FEV ₁ AUC LS mean (SE)	Difference to placebo		
				LS mean (SE)	(95% CI)	p-value
All	-	2.275	-	-	-	-
QAB 150 µg o.d.	84	2.243	0.209 (0.0153)	0.187 (0.0151)	(0.157, 0.216)	<0.001
QAB 75 µg o.d.	86	2.277	0.165 (0.0152)	0.143 (0.0149)	(0.114, 0.173)	<0.001
QAB 55 µg o.d.	85	2.269	0.154 (0.0152)	0.132 (0.0150)	(0.103, 0.162)	<0.001
QAB 27.5 µg b.i.d.	87	2.298	0.143 (0.0151)	0.121 (0.0150)	(0.092, 0.151)	<0.001
QAB 37.5 µg o.d.	84	2.282	0.121 (0.0153)	0.099 (0.0150)	(0.069, 0.128)	<0.001
Placebo	86	2.279	0.022 (0.0152)	-	-	-

(Source: Table 4-2, Clinical Overview)

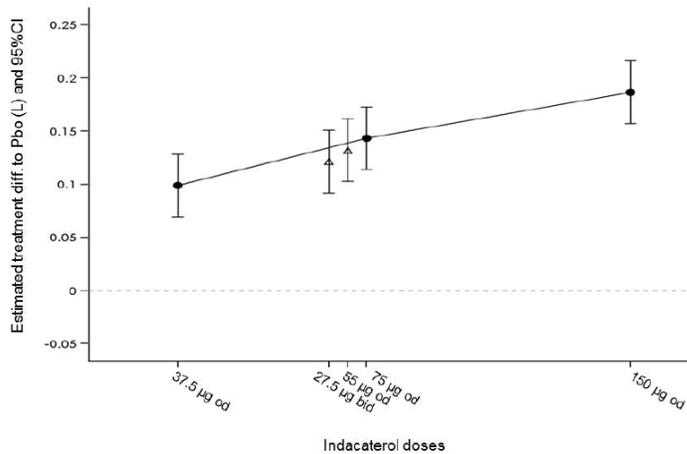


Figure 1. FEV₁ (L) AUC(0-24h) – treatment differences from indacaterol to placebo in Study QVA149A2210

(Source: Figure 4-1, Clinical Overview)

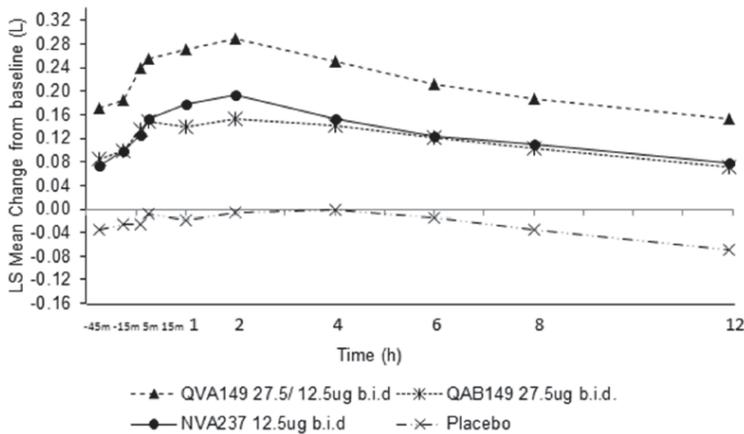
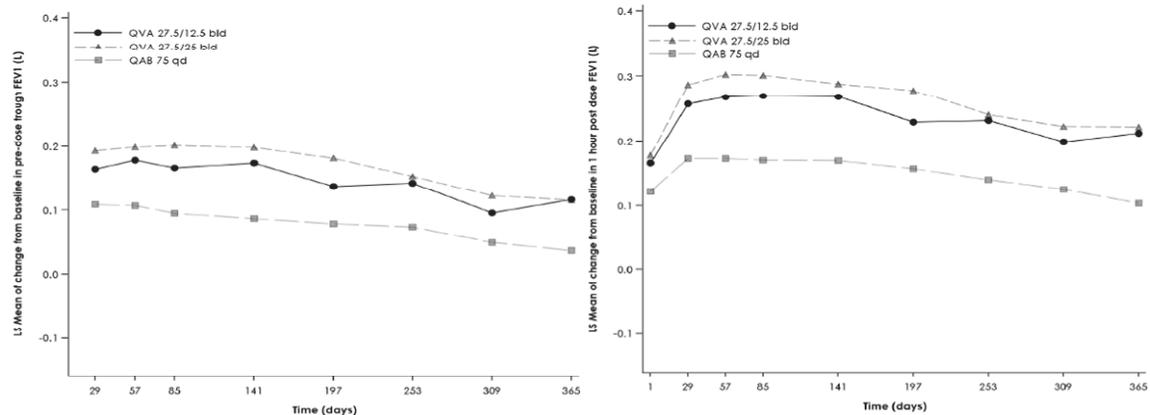


Figure 2. Profile of change from baseline in FEV₁ (L) from 5 min up to 11 h 55 min post-dose on Day 85 (pooled analysis of Studies QVA149A2336 and A2337)

(Source: Figure 4-3, Clinical Overview)



MMRM: Change from baseline in pre-dose trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + airflow limitation severity + region + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Pre-dose trough FEV1 is defined as the mean of FEV1 at -45 min and -15 min before morning dose.

Figure 3. Pre-dose trough FEV1 (L) (left panel) and FEV1 (1 hour post-dose) (right panel), change from baseline, over post-baseline visits in a 52-week Phase 3 study QVA149A2340 in COPD patients

(Source: adapted from Figures 11-1 and 11-2, Study QVA149A2340 report)

Pharmacokinetic Interaction between Indacaterol and Glycopyrrolate

Following multiple BID administration of QVA149 27.5/12.5 mcg (x 2), indacaterol 27.5 mcg (x 2) alone, and glycopyrronium 12.5 mcg (x 2) alone, the steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrronium was similar between the combination product and monotherapies, suggesting there is no PK interaction between the two components (Table 3). Therefore, the relevant findings and/or conclusions of clinical pharmacology studies for the mono-therapies may be extrapolated to QVA149.

Table 3. Comparison of glycopyrrolate and indacaterol PK parameters following BID administration of QVA149 and each drug inhaled alone

Compound	Parameter	Geometric mean ratio (90% CI)
Glycopyrrolate	C _{max,ss}	1.07 (0.97, 1.18)
	AUC _{0-12h,ss}	1.09 (1.05, 1.13)
Indacaterol	C _{max,ss}	0.97 (0.93, 1.02)
	AUC _{0-12h,ss}	0.95 (0.91, 0.99)

(Source: adapted from Tables 11-5 and 11-6, Study QVA149A2107 report)

Pharmacokinetics

- Following oral inhalation from QVA149 inhalation via Concept1 device, both indacaterol and glycopyrronium were rapidly absorbed and reached peak plasma levels (C_{max}) at 15 min and 5 min, respectively. No absolute bioavailability has been performed with QVA149. Food effect for QVA149 is negligible.

- Upon once-daily dosing, steady-state was reached after 12 days for QAB149 and 10 days for NVA237, respectively.
- There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled indacaterol and glycopyrronium based on steady-state exposure.
- There are no clinically relevant differences in steady state systemic exposure to both indacaterol and glycopyrronium between healthy subjects and COPD patients.

Population Pharmacokinetic Analysis

Population PK models were developed for QAB149 and NVA237, respectively, to determine if any intrinsic factors influence the systemic exposure of QAB149 and NVA237 in COPD patients.

QAB149

- Body weight, smoking status, age and sex were identified as major covariates contributing to interpatient variability of indacaterol pharmacokinetics in COPD patients. However, the small magnitude of covariate effects is not considered to be clinically relevant.

NVA237

- Body weight, smoking status, and baseline eGFR were identified as major factors contributing to the interpatient variability of glycopyrronium pharmacokinetics. However, the small magnitude of covariate effects is not considered to be clinically relevant.
- Sex, age, and FEV1 were not statistically significant covariates on CL/F.
- Japanese ethnicity was identified as significant covariate on Vc/F. Simulations indicated that compared to non-Japanese patients with the same body weight, the population mean AUC_{0-24h} in Japanese was similar, and C_{max} in Japanese patients was 76% higher because of a smaller volume of distribution of the central compartment. However, the small magnitude of covariate effects is not considered to be clinically relevant.

Special Populations

No additional studies in special population were submitted in this NDA.

Drug-Drug Interactions (DDI)

Effect of co-administered drugs on glycopyrronium or indacaterol exposure

Following multiple BID administration of QVA149 27.5/12.5 mcg (x 2), indacaterol 27.5 mcg (x 2) alone, and glycopyrronium 12.5 mcg (x 2) alone, the steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrronium was similar between the combination product and monotherapies, suggesting there is no PK interaction between the two components.

Pharmacokinetic/Pharmacodynamic Relationships for Safety

The exposure-response relationships for QT-interval and heart rate were investigated in a thorough QT study and a cardiac safety study. The exposure-response relationship between indacaterol and glycopyrronium plasma concentrations and changes from baseline for QTc showed that with increasing concentrations of either of the analytes, QTc tended to increase and the slopes of linear regression lines were small for both analytes. No relevant exposure-response relationship was observed between the systemic exposure to either indacaterol or glycopyrronium and the heart rate changes.

2. Question Based Review

Only study reports submitted in this NDA will be reviewed in this document. Since there is no PK interaction between indacaterol and glycopyrronium, the relevant findings and/or conclusions for the mono-therapies may be extrapolated to QVA149, including pharmacokinetics, drug interaction, PK in subjects with renal impairment and hepatic impairment. For further details refer to the labeling of ARCAPTA NEOHALER, the Clinical Pharmacology Reviews of NDA22383 (ARCAPTA NEOHALER, Indacaterol Inhalation Powder) by Drs. Sandra S. Sharp and Ying Fan dated 08/25/2009, 09/09/2009, and 02/15/2011, and the Clinical Pharmacology Review of NDA207923 (Glycopyrrolate Inhalation Powder, submitted on 12/29/2014) by Dr. Lei He.

Please note that glycopyrronium is the quaternary ammonium ion ('active moiety') of glycopyrrolate. 15.6 mcg glycopyrrolate is equivalent to 12.5 mcg glycopyrronium. "QVA149 27.5/12.5 mcg indacaterol/glycopyrronium" will be used throughout this review, which is equivalent to the proposed labelled dose "QVA149 27.5/15.6 mcg indacaterol/glycopyrrolate".

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

In vitro studies using human biomaterials were conducted and are listed in Table 4. Study reports DMPK R1100757, R1200048, and R1200049 have been reviewed in NDA207923 (Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis) by Dr. Lei He.

Table 4. In Vitro Studies for QVA149 Using Human Biomaterials

Study/Report name	Objective
DMPK R1100757	Identify hydrolytic enzymes involved in NVA237 metabolism
DMPK R1200048	Potential of NVA237 to inhibit uptake transporter (OAT1, OAT3)
DMPK R1200049	Potential of NVA237 to inhibit uptake transporter (OATP1B1, OATP1B3)
DMPK R1100624	In vitro assessment of cytochrome P450 2A6 and 2B6 enzyme inhibition by QAB149
DMPK R1100625	Assessment of QAB149 as an inhibitor of human organic anion transporting polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3)
DMPK R1100671	Assessment of QAB149 as an inhibitor of human organic anion transporters 1 and 3

The clinical pharmacology studies are summarized in Table 5.

Table 5. Summary of Clinical Pharmacology studies

		Study ID	Objectives	Population	Dosing Regimen	Device
Comparative BA/BE study in HV	1	QVA149A2101	PK, Safety	HVs (28)	QAB149 300 mcg NVA237 100 mcg QVA149 300/100 mcg	Concept 1
	2	QVA149A2103	PK, Safety	HVs (42)	QAB149 150 mcg QD for 14 days NVA237 50 mcg QD for 14 days QVA149 150/50 mcg QD for 14 days	Concept 1
	3	QVA149A2106	Comparative PK	HVs (24)	QAB149 150 mcg QD for 14 days NVA237 50 mcg QD for 14 days QVA149 110/50 mcg QD for 14 days	Concept 1
	4	QVA149A2107	PK interaction between NVA237 and QAB149	HVs (36)	QAB149 27.5 mcg ×2 BID for 14 days NVA237 12.5 mcg ×2 BID for 14 days QVA149 27.5/12.5 mcg ×2 BID for 14 days	Concept 1
Intrinsic factor PK study	5	QVA149A1101	PK, Safety	Caucasian and Japanese (48)	QVA149 110/50 mcg QVA149 220/100 mcg	Concept 1
	6	QVA149A2104	PK, safety	Chinese (12)	QVA 110/50 mcg QD for 14 days	Concept 1
PD, PK/PD study in HV	7	QVA149A2105	PD (heart rate, serum potassium) safety, PK	HVs (50)	QVA149 440/200mcg QAB149 600 mcg NVA237 200 mcg Salmeterol 200 mcg	Concept 1 and Diskus (for PC)
	8	QVA149A2109	PD (QT interval), safety, PK	HVs (84)	QVA149 55/50 mcg Moxifloxacin 400 mg, oral	Concept 1
PD, PK/PD in asthma patient	9	QVA149A2210	Dose ranging, efficacy, PK	Asthma (91)	QAB149 37.5, 55, 75, 150 mcg QD; QAB149 27.5 mcg BID	Concept 1
Efficacy and safety study in COPD patients	10	QVA149A2336	Efficacy, safety, PK	COPD (1042)	QVA149 27.5/12.5 mcg BID	Concept 1
	11	QVA149A2337	Efficacy, safety, PK	COPD (1001)	QAB 149 27.5 mcg BID NVA237 12.5 mcg BID	Concept 1

*HVs: healthy volunteers; SD: single dose; MD: multiple dose; QD: once daily; BID: twice daily; BA: bioavailability; PC: positive control

Key clinical studies supporting QVA149 (b)(4) mcg BID dosing regimen are summarized in Table 6.

Table 6. Overview of Clinical Development Program

Relative bioavailability	QVA149A2107	HVs (36) QAB149 27.5 mcg ×2 BID NVA237 12.5 mcg ×2 BID QVA149 27.5/12.5 mcg ×2 BID
Thorough QT study	QVA149A2109	HVs (84) QVA149 440/400 mcg
Dose ranging study	QVA149A2210	Asthma (91) QAB149 37.5, 55, 75, 150 mcg QD; QAB149 27.5 mcg BID
Pivotal phase 3 studies	QVA149A2336	COPD (1042), 12w QVA149 27.5/12.5 mcg BID monotherapy placebo
	QVA149A2337	COPD (1001), 12w QVA149 27.5/12.5 mcg BID monotherapy placebo
	QVA149A2340	COPD (615), 52w QVA149 27.5/12.5 mcg BID QAB149 75 mcg QD

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

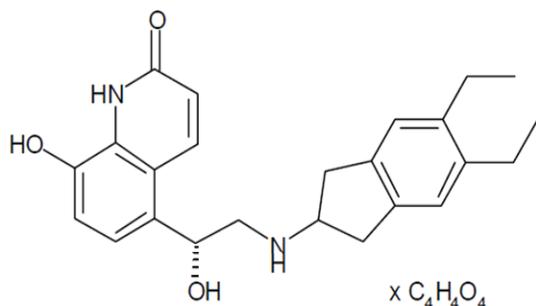
Drug Substance

Indacaterol maleate (QAB149) and glycopyrronium bromide (NVA237, described in the Ph. Eur and USP as glycopyrrolate) are both small molecule drugs. Their structures are shown in Figure 4.

Indacaterol maleate is a white to very slightly grayish or very slightly yellowish powder. Its molecular formula is $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$ and the molecular weight is 392.49 g/mol (free base) and 508.56 g/mol (maleate salt). It is very slightly soluble to insoluble in an aqueous environment and is slightly to very slightly insoluble in alcohols.

Glycopyrronium bromide is a white powder with a molecular formula of $C_{19}H_{28}NO_3 \cdot Br$ and the molecular weight is 398.33. It has a melting range of 193 – 198°C and is freely soluble in water.

Indacaterol Maleate



Glycopyrronium Bromide

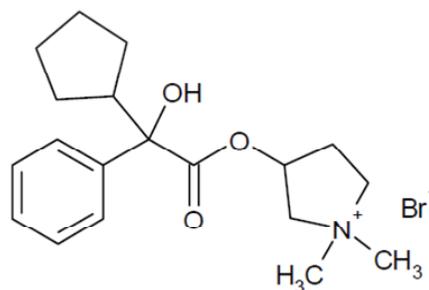


Figure 4. Molecular Structure of indacaterol maleate and glycopyrronium bromide
(Source: Table 1-1, Summary of Biopharmaceutic Studies)

Drug Product

The drug product, Indacaterol /Glycopyrrolate inhalation powder capsule inhalation powder hard capsule is a white to practically white powder contained in a hypromellose capsule size 3 with yellow transparent cap and uncolored transparent body with imprint, administered via the Concept1 unit dose dry powder inhaler designed to deliver single doses for oral inhalation.

One Indacaterol /Glycopyrrolate inhalation powder capsule contains (b) (4) mcg of indacaterol maleate (corresponding to 27.5 mcg of indacaterol) and 15.6 mcg of glycopyrronium bromide (glycopyrrolate) (corresponding to 12.5 mcg glycopyrronium). The composition of drug product is shown in Table 7.

Table 7. Composition of Indacaterol/Glycopyrrolate inhalation powder capsule

Ingredient	Amount per capsule (mg)	Function	Reference to standards
Capsule fill			
Indacaterol maleate (QAB149)	(b) (4) ¹	Drug substance	Novartis monograph
Glycopyrronium bromide (NVA237)	0.0156 ²	Drug substance	Novartis monograph
Lactose monohydrate	24.9112	(b) (4)	Ph. Eur., USP/NF, Novartis monograph ³
Magnesium stearate	0.0375	(b) (4)	Ph. Eur., USP/NF, Novartis monograph ⁴
Capsule fill weight	(b) (4)		
Empty capsule shell, pre-printed			
Capsule shell (theoretical weight)	(b) (4)		See Table 1-3
Printing Ink, black	(b) (4)		See Table 1-4
Total capsule weight	74.00		

¹ Corresponds to 27.5 mcg QAB149 active moiety (target delivered dose of (b) (4) mcg).

² Corresponds to 12.5 mcg NVA237 active moiety (target delivered dose of (b) (4) mcg).

³ Novartis monograph contains additional tests as provided in Section [3.2.P.4.1_lactose]

⁴ Novartis monograph contains additional tests as provided in Section [3.2.P.4.1_mgsterate]

(Source: Table 1-2, Drug Product (2.3.P))

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Indacaterol /Glycopyrrolate Inhalation Powder (QVA149) is a fixed-dose combination (FDC) of a long-acting β 2-adrenergic agonist (LABA) (indacaterol, QAB149) and a long-acting muscarinic antagonist (LAMA) (glycopyrronium bromide, NVA237).

Indacaterol /Glycopyrrolate Inhalation Powder is proposed for “*the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema*”.

2.2.3 What are the proposed dosages and routes of administration?

The recommended dosage of Indacaterol /Glycopyrrolate Inhalation Powder is the inhalation of the contents of one QVA149 (indacaterol 27.5 mcg /glycopyrronium 12.5 mcg) capsule twice-daily using the NEOHALER device.

QVA149 should be administered at the same time of the day, (1 capsule in the morning and 1 capsule in the evening), every day. More frequent administration or a greater number of inhalations (more than 1 capsule twice-daily) of QVA149 is not recommended.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for treatment of COPD in the United States can be classified into the following classes:

1. Bronchodilators

- β 2 agonist:
 - long acting: salmeterol, formoterol, arformoterol, indacaterol etc.
 - short acting: salbutamol, albuterol, terbutaline etc.
- Anticholinergics:
 - long acting: tiotropium, aclidinium , umeclidinium
 - short acting: ipratropium
- Methylxanthine: theophylline
- Combination: albuterol+ipratropium (Combivent, Duoneb), umeclidinium +vilanterol (Anoro Ellipta)

2. Corticosteroids

- Oral corticosteroids
- ICS
- Combination:
 - salmeterol+fluticasone (Advair)
 - formoterol+budesonide (Symbicort)
 - Vilanterol +fluticasone furoate (Breo)

3. Other medications

- Long acting PDE-4 inhibitor: roflumilast (Daliresp)
- Antibiotics

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The QVA149 development program includes full characterization (dose-ranging) of the individual components (NVA237 and QAB149) to establish the appropriate dose for each component, before proceeding to the QVA149 Phase 3 studies. One dosing regimen, QVA149 27.5/12.5 mcg BID was selected for further evaluation in Phase 3 program.

NVA237

Two dose ranging studies were conducted and NVA12.5 mcg BID was selected as the dosing regimen for NVA237 monotherapy (NDA207923) and NVA237 in the FDC product QVA149.

- Study NVA237A2205 is a randomized, double-blind, placebo-controlled, 4-period incomplete block cross-over study with an active control arm in COPD patients. The evaluated dosing regimens of NVA237 include:
 - QD: 12.5, 25, 50, and 100 mcg
- Study NVA237A2208 is a randomized, double-blind, placebo-controlled, 2-period, cross-over study in COPD patients. The evaluated dosing regimens of NVA237 include:
 - QD: 12.5, 25, 50, 100 mcg
 - BID: 12.5, 25, 50 mcg

QAB149

One dose ranging study was conducted and QB149 27.5 mcg BID was selected as the dosing regimen for QAB149 in QVA149.

- Study QVA149A2210 is a randomized, double-blind, placebo-controlled crossover study in patients with persistent asthma. The evaluated dosing regimens of QAB149 include:
 - QD: 37.5, 55, 75, 150 mcg
 - BID: 27.5 mcg

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Sponsor has used trough FEV1 and FEV1 AUC_{0-24h} as the primary endpoints in Phase II dose ranging/regimen selection studies for NVA237 and QAB149, respectively. The change from baseline in FEV1 AUC_{0-12h} at week 12 is the primary endpoints for the primary Phase 3 efficacy studies (Studies QVA149A 2336 and A2337). These endpoints have also been used in the development program of other drugs for COPD.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameter and exposure

response relationships?

In all relevant studies, only glycopyrronium and indacaterol concentrations were measured. No metabolites were quantified because the metabolites of NVA237 and QAB149 are not active and are not associated with efficacy or safety.

2.4 Exposure-Response

2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

For inhaled QAB149 and NVA237, the systemic exposure is not directly related to clinical response (FEV1).

2.4.2 Has the dosing of QVA149 been adequately explored?

The dosing regimen of QVA149 has been adequately explored in Phase 2 trials. This application includes dose-ranging information for NVA237 in COPD, as well as dose-ranging information for QAB149 in asthma. As a result, one dosing regimen, QVA149 27.5/12.5 mcg BID, was tested in Phase III studies in COPD patients.

NVA237

Two dose ranging trials for NVA237 were conducted in COPD patients. In study NVA237A2208, both QD (12.5, 25, 50, and 100 mcg) and BID (12.5, 25, and 50 mcg) dosing regimens were explored. At Day 28, all NVA237 doses had a higher mean trough FEV1 when compared to placebo and the differences were statistically significant. Furthermore, at Day 28, the NVA237 12.5 mcg BID dose was the lowest dose with a clinically important (>0.100 L) difference compared to placebo (0.139 L) and that difference was statistically significant (<0.001) (Table 8).

Table 8. Mean change from baseline in trough FEV1 for NVA237 (QD vs BID) in Study NVA237A2208

NVA237 dose	n	LS Mean (SE) in trough FEV ₁ (L)	Comparison to Placebo		
			LS Mean (SE)	95% CI	p-value
12.5 µg o.d.	81	1.329 (0.0193)	0.083 (0.0271)	(0.030, 0.136)	0.002
25 µg o.d.	88	1.344 (0.0188)	0.098 (0.0256)	(0.048, 0.148)	<0.001
12.5 µg b.i.d.	90	1.385 (0.0185)	0.139 (0.0254)	(0.089, 0.189)	<0.001
50 µg o.d.	88	1.336 (0.0187)	0.090 (0.0264)	(0.038, 0.142)	<0.001
25 µg b.i.d.	87	1.414 (0.0187)	0.167 (0.0265)	(0.115, 0.219)	<0.001
100 µg o.d.	90	1.423 (0.0186)	0.176 (0.0223)	(0.132, 0.220)	<0.001
50 µg b.i.d.	81	1.423 (0.0194)	0.177 (0.0229)	(0.132, 0.222)	<0.001
Placebo	82	1.246 (0.0194)	-	-	-

(Source: Table 4-2 Clinical overview, NDA207923)

QAB149

One dose-ranging trial for QAB149 was conducted in patients with persistent asthma. All 5 QAB149 doses (27.5 mcg BID, 37.5 mcg QD, 55 mcg QD, 75 mcg QD, and 150 mcg

QD) showed statistically significant improvements in both primary and secondary endpoints vs. placebo: FEV₁ AUC(0-24h) (Table 9), trough FEV₁, peak FEV₁, and FVC AUC(0-24h). Estimated treatment differences of change from period baseline in FEV₁ AUC(0-24h) showed a dose-ordered response with clear separation of doses for all treatment groups compared to placebo (Figure 5).

Table 9. Change from period baseline in FEV₁ (L) AUC(0-24h) - Study QVA149A2210

Treatment	n	FEV ₁ AUC (L) Baseline Raw Means	Change from BL in FEV ₁ AUC LS mean (SE)	Difference to placebo		
				LS mean (SE)	(95% CI)	p-value
All	-	2.275	-	-	-	-
QAB 150 µg o.d.	84	2.243	0.209 (0.0153)	0.187 (0.0151)	(0.157, 0.216)	<0.001
QAB 75 µg o.d.	86	2.277	0.165 (0.0152)	0.143 (0.0149)	(0.114, 0.173)	<0.001
QAB 55 µg o.d.	85	2.269	0.154 (0.0152)	0.132 (0.0150)	(0.103, 0.162)	<0.001
QAB 27.5 µg b.i.d.	87	2.298	0.143 (0.0151)	0.121 (0.0150)	(0.092, 0.151)	<0.001
QAB 37.5 µg o.d.	84	2.282	0.121 (0.0153)	0.099 (0.0150)	(0.069, 0.128)	<0.001
Placebo	86	2.279	0.022 (0.0152)	-	-	-

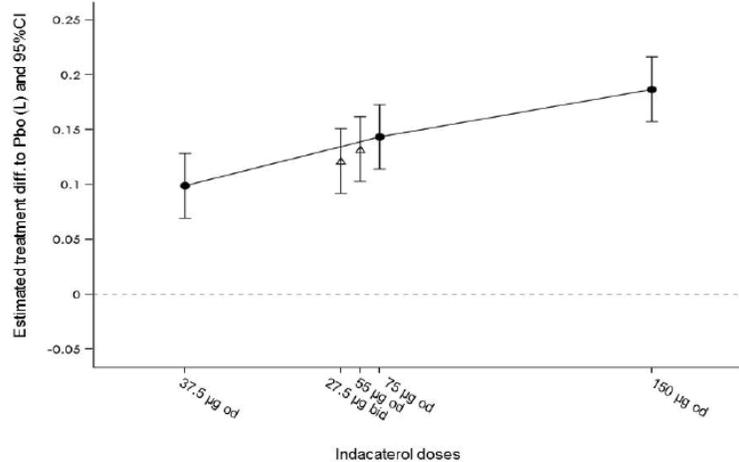
AUC = area under the curve; CI = confidence interval; BL = baseline; FEV₁ = forced expiratory volume in 1 sec; LS mean = least squares mean; LMM: CFB in AUC = treatment + period + overall mean baseline FEV₁ + period adjusted baseline correction + random effect of patient; SE = standard error of the mean.

The overall mean baseline FEV₁ (2.275) is the average of the 6 period baselines and is the baseline mean in the LS mean change from baseline values. Each period baseline FEV₁ is the mean of the -45 min and -15 min FEV₁ values taken on Day 1 prior to first dose in the respective period.

The period adjusted baseline correction is the deviation of a patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.

Source: [SCE-Table 4-1]

(Source: Table 4-2, Clinical Overview)



bid = twice daily; diff. = difference; od = once daily; Pbo = placebo; FAS = full analysis set; FEV₁ = forced expiratory volume in 1 sec.

Note: filled circles denote the arithmetic dose progression of indacaterol doses from 37.5 to 150 µg; clear triangles denote (b) (4) d. (55 µg) and b.i.d. (27.5 µg).

LMM: CFB in AUC = treatment + period + overall mean baseline FEV₁ + period adjusted baseline correction + random effect of patient.

The overall mean baseline FEV₁ is the average of the 6 period baselines. Each period baseline FEV₁ is the mean of the -45 min and -15 min FEV₁ values taken on Day 1 prior to first dose in the respective period.

The period adjusted baseline correction is the deviation of a patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.

Source: [SCE-Figure 4-2]

Figure 5. FEV₁ (L) AUC(0-24h) – treatment differences from indacaterol to placebo in Study QVA149A2210

(Source: Figure 4-1, Clinical Overview)

Overall, dose-ranging data for NVA237 in COPD patients supported efficacy for 12.5 mcg BID dosing regimen carried forward for confirmation in the Phase 3 COPD

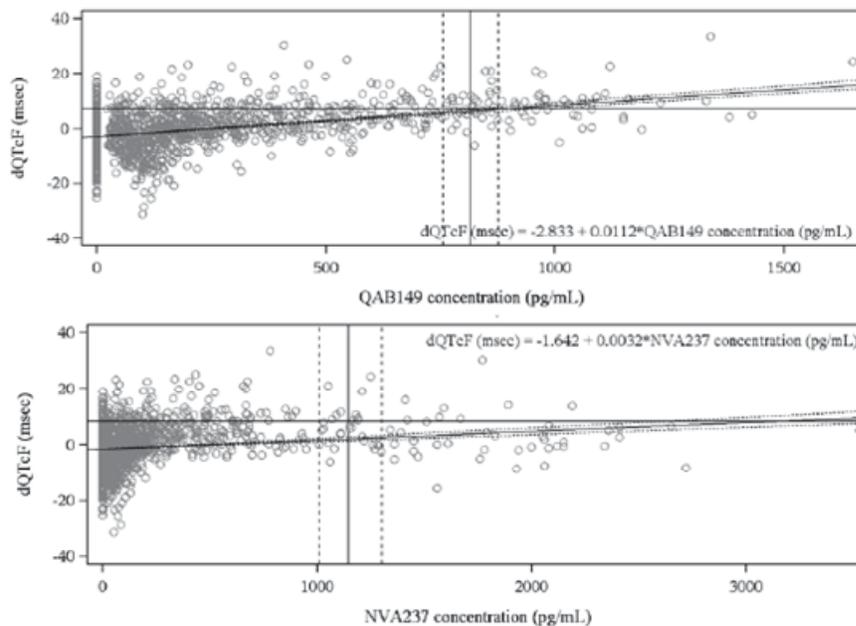
program. In terms of QAB149, dose-ranging data in asthma patients supported the QAB149 dose of 27.5 mcg BID for the Phase 3 trials of the combination product.

2.4.3 What are the characteristics of the exposure-response relationships for safety?

The exposure-response relationships for QT-interval and heart rate (HR) were investigated in Study QVA149A2109, a thorough QT study, and Study QVA149A2105, a cardiac safety study.

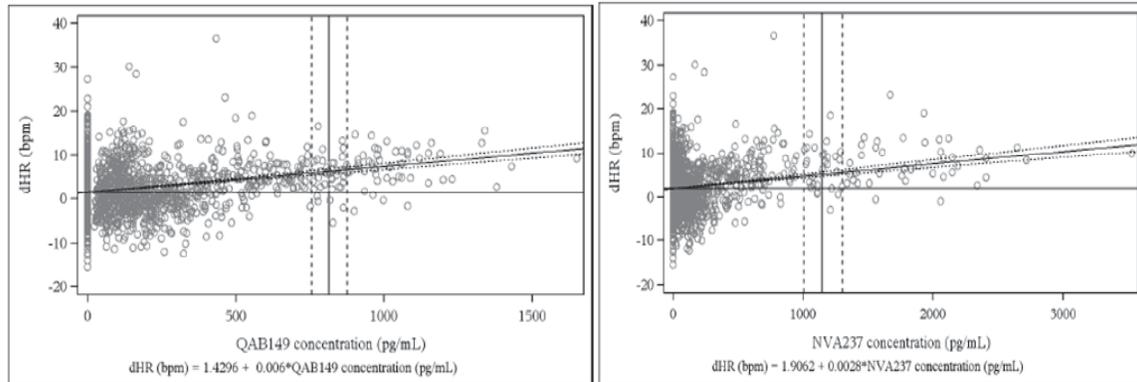
In Study QVA149A2109, the exposure-response relationship between indacaterol and glycopyrronium plasma concentrations and changes from baseline for QTc showed that with increasing concentrations of either of the analytes, QTc tended to increase. The slopes of linear regression lines were small for both analytes (Figures 6). No relevant exposure-response relationship was observed between the systemic exposure to either indacaterol or glycopyrronium and the HR changes (Figure 7).

In Study QVA149A2105, there was no apparent relationship observed between drug concentrations and changes of heart rate or QTc interval, respectively.



The solid regression line describes a linear relationship between QVA149 or 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. The vertical lines are the geometric mean and 95% confidence limits for Cmax.

Figure 6. QAB149 plasma concentrations and corresponding change from baseline in QTcF
(Source: Adapted from Figures 11-5 and 11-6 of Study QVA149A2109 report)



The solid regression line describes the linear relationship between QAB149 or 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 the estimated intercept. The vertical lines are the geometric mean and 95% confidence limits for C_{max} .

Figure 7. QAB149 and NVA237 plasma concentrations and corresponding change from baseline in HR (dHR)

(Source: Adapted from Figures 11-7 and 11-8 of Study QVA149A2109 report)

2.4.4 Does this drug prolong QT/QTc Interval?

The effect of QVA149 on the QTcF-interval was evaluated in a randomized, partially-blinded, single dose, placebo and positive (moxifloxacin) controlled, three period cross-over study in HVs (QVA1492109). Healthy subjects received single supra-therapeutic oral inhaled dose of QVA149 440/400 mcg, placebo, and a single oral dose of moxifloxacin 400 mg. The estimated mean maximal change from baseline in QTcF vs. placebo was 9.18 ms with an upper bound of the 2-sided 90% CI of 10.46 ms at 30 min postdose. At all other time-points the upper bound of the 90%-confidence limit was below 10 ms and therefore within the threshold for regulatory concern as described in ICH E14 guideline.

For further details refer to QT/IRT review for NDA207930.

2.5 What are the PK characteristics of the drug?

As stated above, for QVA149, some PK information of both components, including drug absorption, distribution, metabolism and elimination was extrapolated from PK studies with monotherapies (summarized as below).

QAB149

- “Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol based on AUC_{24h} was 2.9 to 3.8 for QD inhaled doses between 75 mcg and 600 mcg.
- After IV infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557 L indicating an extensive distribution. The in vitro human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively. UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with

recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is the predominant isoenzyme responsible for hydroxylation of indacaterol. Indacaterol is a low affinity substrate for the efflux pump P-gp. After oral administration of radiolabelled indacaterol, unchanged indacaterol was the main component in serum, accounting for about one-third of total drug-related AUC over 24 hours. 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.

- *In human, the amount of indacaterol excreted unchanged via urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 L/h and 1.20 L/h. When compared with the serum clearance of indacaterol of 18.8 L/h to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2% to 6% of systemic clearance) in the elimination of systemically available indacaterol.*
- *Following indacaterol oral dosing, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with greater than or equal to 90% of the dose recovered in the excreta. Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing ranged from 40 to 56 hours which is consistent with the observed time to steady state of approximately 12 to 15 days.”*

NVA237

- Following oral inhalation of NVA237 via Concept 1 device, the absolute bioavailability of glycopyrronium is estimated to be ~40%, of which 90% systemic exposure is due to lung absorption and 10% is due to gastrointestinal absorption. Food effect for NVA237 would be negligible. C_{max} was reached at 5 minutes for glycopyrronium following NVA237 inhalation. The glycopyrronium PK is approximately linear within the dose range of 12.5 to 200 mcg. Upon QD dosing, steady-state was reached within one week.
- The in vitro human plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL. After IV dosing, the steady-state volume of distribution (V_{ss}) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (V_z) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (V_z/F) was 7310 L.
- Glycopyrronium is a substrate for the cationic SLC transporter OCT2 and MATE1. Glycopyrronium does not significantly inhibit or induce CYP450 enzymes, ABC transporters or solute carriers at therapeutic concentrations, suggesting the potential of relevant drug-drug interactions appears to be low.
- Renal elimination of parent drug accounts for ~60-70% of systemic clearance. Metabolism and bile excretion account for the non-renal elimination. The

apparent elimination half-life of glycopyrronium following oral inhalation administration was ~33-53 h.

For further details refer to ARCAPTA NEOHALER labeling, the Clinical Pharmacology Reviews of NDA22383 (ARCAPTA NEOHALER, Indacaterol Inhalation Powder) by Drs. Sandra S. Sharp and Ying Fan dated 08/25/2009, 09/09/2009, and 02/15/2011, and the Clinical Pharmacology Review of NDA207923 (Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis) by Dr. Lei He.

The relevant information based on the studies submitted in this NDA is summarized below.

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK

The single dose PK of QVA149 was investigated in Study QVA149A1101 with single inhalation of QVA149 110/50 mcg and 220/100 mcg in Japanese and Caucasian HVs. The mean plasma concentration-time profile is shown in Figure 8 and the summary of PK parameters is shown in Table 10. Following oral inhalation, C_{max} of QAB149 and NVA237 was reached at 15min and 5 min (T_{max}), respectively. Following QVA149 inhalation at 110/50 mcg and 220/100 mcg, the systemic exposure of QAB149 and NVA237 are slightly higher in Japanese compared to Caucasians (Table 11). However, it was not considered clinically relevant.

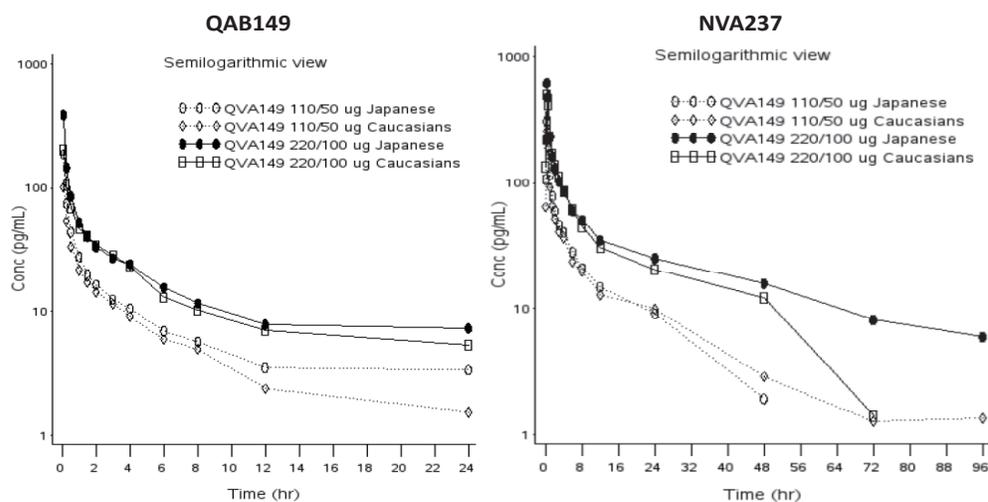


Figure 8. Arithmetic mean plasma concentration-time profiles of QAB149 and NVA237
(Adapted from Figures 11-1 and 11-2, Study QVA149A1101 report)

Table 10. Summary of primary PK parameters of QAB149 and NVA237

Analyte and Treatment	Ethnicity	AUCIast	AUC0-24h	Cmax	Tmax
		(pg·h/mL) N=8	(pg·h/mL) N=8	(pg/mL) N=8	(h) N=8
Indacaterol					
QVA149 110/50 µg	Japanese	731 (243) 33.2%	703 (177) 25.2%	309 (75.4) 24.4%	0.25 (0.25-0.25)
	Caucasians	748 (487) 65.1%	614 (234) 38.1%	257 (101) 39.5%	0.25 (0.25-0.25)
QVA149 220/100 µg	Japanese	2440 (589) 24.2%	1570 (312) 19.9%	620 (158) 25.5%	0.25 (0.25-0.25)
	Caucasians	1860 (600) 32.3%	1450 (493) 34.0%	511 (149) 29.2%	0.25 (0.25-0.50)
Glycopyrronium					
QVA149 110/50 µg	Japanese	196 (70.6) 36.0%	200 (65.6) 32.9%	186 (83.4) 44.8%	0.083 (0.083-0.083)
	Caucasians	139 (53.3) 38.3%	147 (48.0) 32.6%	101 (46.8) 46.2%	0.083 (0.083-0.083)
QVA149 220/100 µg	Japanese	419 (106) 25.4%	419 (106) 25.4%	389 (166) 42.8%	0.083 (0.083-0.083)
	Caucasians	352 (88.6) 25.2%	352 (88.6) 25.2%	203 (106) 52.4%	0.083 (0.083-0.083)

AUCIast, AUC0-24h, Cmax: Upper line, Arithmetic Mean (SD); Lower line, CV%
Tmax: Median (Range)

Source: [QVA149A1101 – Table 11-2]

(Source: Table 11-2, Study QVA149A1101 report)

Table 11. QAB149 and NVA237 PK comparison between Japanese and Caucasians

Treatment	Analyte	Parameter (unit)	Geometric mean		Ratio (J/C)	90% CI
			Japanese	Caucasian		
QVA149 110/50 µg	QAB149	AUCIast (pg·h/mL)	691.7	609.2	1.14	(0.57, 2.27)
		AUC0-24h (pg·h/mL)	681.8	559.2	1.22	(0.73, 2.05)
		Cmax (pg/mL)	299.9	237.9	1.26	(0.77, 2.07)
	NVA237	AUCIast (pg·h/mL)	179.5	129.4	1.39	(0.80, 2.41)
		AUC0-24h (pg·h/mL)	185.6	139.5	1.33	(0.80, 2.21)
		Cmax (pg/mL)	162.9	91.6	1.78	(0.77, 4.11)
QVA149 220/100 µg	QAB149	AUCIast (pg·h/mL)	2366.1	1766.4	1.34	(0.67, 2.68)
		AUC0-24h (pg·h/mL)	1534.0	1385.2	1.11	(0.66, 1.86)
		Cmax (pg/mL)	599.6	489.8	1.22	(0.75, 2.01)
	NVA237	AUCIast (pg·h/mL)	408.4	342.5	1.19	(0.68, 2.08)
		AUC0-24h (pg·h/mL)	408.4	342.5	1.19	(0.72, 1.98)
		Cmax (pg/mL)	344.9	179.4	1.92	(0.83, 4.45)

Source: Post-text table 14.2-1.4

(Source: Table 11-3, Study QVA149A1101 report)

Multiple dose PK

Multiple dose PK of NVA237 was characterized in Chinese HVs in Study QVA149A2104. The PK profiles and PK parameters of QAB149 and NVA237 are shown in Figures 9 and Table 12 and 13.

QAB149: Following QVA149 (110/50 mcg) inhalation, Tmax of QAB149 was 15 min post dose after both single and multiple QD dose. QAB149 plasma concentrations showed a steep decrease for up to 4-8 hours and a slower decrease thereafter. The observed accumulation ratio (Racc) of the AUC0-24h (Day14/Day1) was 3.02 ± 0.543 . The estimated mean accumulation ratio of Cmax from Day 1 to Day 14 was ~ 1.56 . The terminal elimination half-life (T1/2) could not be accurately determined because the individual plasma concentration-time profiles did not show a continuous decline in plasma concentrations during the terminal phase. QAB149 PK steady-state conditions were reached after 12 days of daily dosing with QVA149.

NVA237: Following QVA149 (110/50 mcg) inhalation, T_{max} of NVA237 was 5 min post dose after both single and multiple QD dose. NVA237 plasma concentrations showed a steep decrease for up to 4-8 hours and a slower decrease thereafter. The observed accumulation ratio (R_{acc}) of the AUC_{0-24h} (Day14/Day1) was 2.94 ± 0.686. The estimated mean accumulation ratio of C_{max} from Day 1 to Day 14 was ~1.33. The terminal elimination half-life (T_{1/2}) could not be accurately determined because the individual plasma concentration-time profiles did not show a continuous decline in plasma concentrations during the terminal phase. NVA237 PK steady-state conditions were reached after 10 days of daily dosing with QVA149.

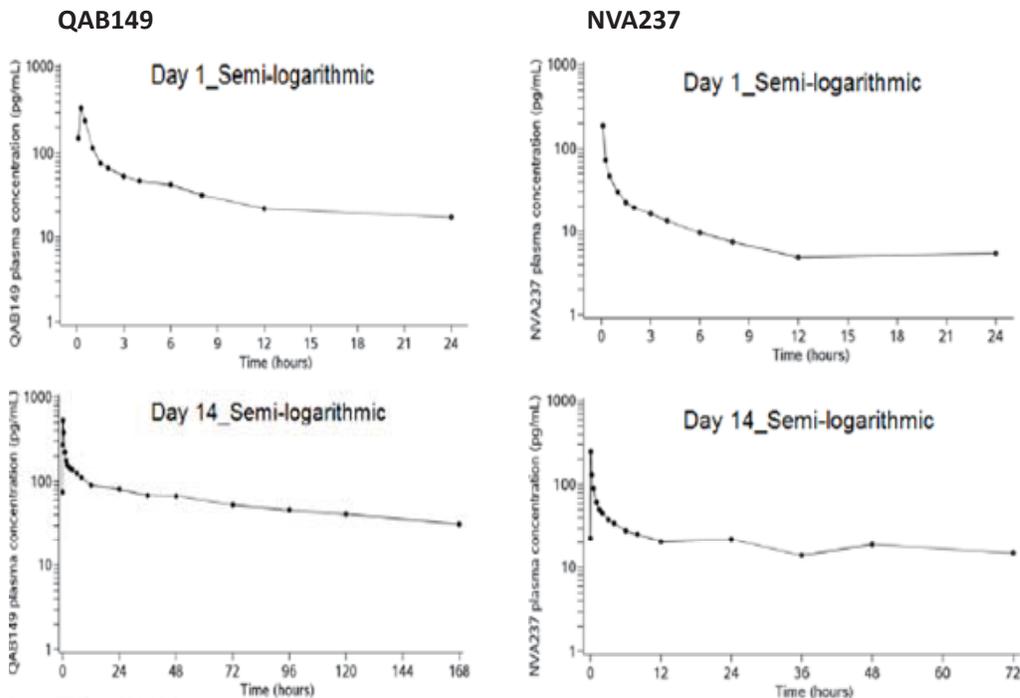


Figure 9. Mean plasma concentration-time profiles of QAB149 (left) and NVA237 (right) on Day 1 and Day 14

(Source: adapted from Figures 11-1 and 11-2, Study QVA149A2104 report)

Table 12. Summary of PK parameters of QAB149 and NVA237 on Day 1

PK parameter (unit)	QAB149	NVA237
	Mean ± SD (% CV) [n]	Mean ± SD (% CV) [n]
AUC _{0-24h} (hr*pg/mL)	907 ± 185 (20.4) [12]	246 ± 68.9 (28.0) [12]
C _{max} (pg/mL)	339 ± 80.2 (23.7) [12]	187 ± 75.0 (40.2) [12]
T _{max} (hr)*	0.25 (0.25-0.25) [12]	0.08 (0.08-0.08) [12]

Source: [Table 14.2-2.1](#) and [Table 14.2-2.2](#)

*Median (Min - Max) [n]

(Source: Table 11-2, Study QVA149A2104 report)

Table 13. Summary of PK parameters of QAB149 and NVA237 on Day 14

PK parameter (unit)	QAB149	NVA237
	Mean ± SD (% CV) [n]	Mean ± SD (% CV) [n]
C _{min,ss} (pg/mL)	73.5 ± 15.7 (21.3) [11]	19.3 ± 6.44 (33.4) [11]
C _{max,ss} (pg/mL)	528 ± 156 (29.5) [11]	248 ± 96.8 (39.0) [11]
AUC _{0-24h,ss} (hr*pg/mL)	2750 ± 616 (22.4) [11]	698 ± 211 (30.3) [11]
T _{max} (hour)*	0.25 (0.25-0.25) [11]	0.08 (0.08-0.08) [11]
C _{av,ss} (pg/mL)	114 ± 25.7 (22.4) [11]	29.1 ± 8.80 (30.3) [11]
T _{1/2,acc} (hr)	41.3 ± 9.17 (22.2) [11]	40.0 ± 11.6 (29.0) [11]
R _{acc}	3.02 ± 0.543 (18.0) [11]	2.94 ± 0.686 (23.3) [11]
Fluc (%)	393 ± 51.9 (13.2) [11]	778 ± 139 (17.9) [11]

Source: [Table 14.2-2.3](#) and [Table 14.2-2.4](#)

*Median (Min - Max) [n]

(Source: Table 11-3, Study QVA149A2104 report)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Overall, there are no clinically relevant differences in steady state systemic exposure to both indacaterol and glycopyrronium between healthy subjects and COPD patients (Table 14).

Table 14. Summary of steady state PK parameters of indacaterol and glycopyrrolate following QVA149 27.5/12.5 mcg BID dosing in COPD patients and healthy volunteers

Study and analyte	Population	C _{max,ss} [pg/mL]	AUC _{0-24h,ss} [pg.h/mL]
Indacaterol			
QVA149A2107 ¹⁾	Healthy subjects	92.0 (19.2)	960 (210)
PopPK QVA149 27.5/12.5 µg b.i.d	COPD patients	72.7 (26.1)	1328 (500)
Glycopyrronium			
QVA149A2107 ¹⁾	Healthy subjects	37.8 (11.9)	243 (52.4)
PopPK QVA149 27.5/12.5 µg b.i.d	COPD patients	30.4 (17.1)	299 (128)

Note: PK parameters: Arithmetic mean (SD)

¹⁾ Derived from a b.i.d. dosing of QVA149 27.5/12.5 x 2 in healthy volunteers: C_{max,ss} was divided by 2 and AUC_{0-24h} given based on AUC_{0-12h} (see [Section 2.2.7](#)).

(Source: Table 3-1, Summary of Clinical Pharmacology)

2.5.3 What are the characteristics of drug absorption?

No absolute bioavailability has been performed with QVA149 27.5/12.5 mcg.

The estimates of the absolute bioavailability following inhalation of each of the monotherapy of indacaterol and glycopyrronium with the Concept1 are about 45% and 40%, respectively.

2.5.11 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality for indacaterol and glycopyrronium after QVA149 27.5/12.5 mcg BID and 110/50 mcg QD was assessed as part of the pooled population PK analysis of QVA149. Results indicate that the pharmacokinetics of indacaterol and glycopyrronium in the FDC were dose proportional.

- Indacaterol: following QVA149 27.5/12.5 mcg BID, the AUC_{0-24h,ss} of indacaterol is approximately half of that after QVA149 110/50 mcg QD. C_{max,ss} of indacaterol was ~3 times lower after QVA149 27.5/12.5 mcg BID regimen compared to after QVA149 110/50 mcg QD.
- Glycopyrronium: following QVA149 27.5/12.5 mcg BID, the AUC_{0-24h,ss} of glycopyrronium is about half of that after QVA149 110/50 mcg QD. C_{max,ss} of glycopyrronium was ~3.5 times lower after QVA149 27.5/12.5 mcg BID regimen compared to after QVA149 110/50 mcg QD.

In Study QVA149A1101 in Japanese and Caucasians, following single inhalation of QVA149 110/50 mcg and 220/100 mcg, mean C_{max} of indacaterol and glycopyrronium appeared to increase dose proportionally in both ethnic groups (2-fold). The increase in mean AUC_{0-24h} and AUC_{last} with doubling the dose, ranged from 2.1-fold to 2.4-fold and 2.14-fold and 3.34-fold, respectively across ethnic groups. (See Section 2.5.1)

2.5.12 How do the PK parameters change with time following chronic dosing?

Multiple dose PK of NVA237 was characterized in Chinese HVs in Study QVA149A2104.

QAB149: T_{max} of QAB149 was 15 min post dose after both single and multiple QD QVA149 dose. Following repeated QVA149 (110/50 mcg) QD inhalation, QAB149 PK steady-state conditions were reached after 12 days. The observed accumulation ratio (R_{acc}) of the AUC_{0-24h} (Day14/Day1) was 3.02 ± 0.543. The estimated mean accumulation ratio of C_{max} from Day 1 to Day 14 was ~1.56.

NVA237: T_{max} of NVA237 was 5 min post dose after both single and multiple QD QVA149 dose. Following repeated QVA149 (110/50 mcg) QD inhalation, NVA237 PK steady-state conditions were reached after 10 days. The observed accumulation ratio (R_{acc}) of the AUC_{0-24h} (Day14/Day1) was 2.94 ± 0.686. The estimated mean accumulation ratio of C_{max} from Day 1 to Day 14 was ~1.33.

2.5.13 Is there evidence for a circadian rhythm of the PK?

The circadian rhythm of QVA149 PK was not evaluated in this NDA.

2.6 Intrinsic Factors

As stated above, for QVA149, the PK information in subjects with renal impairment and hepatic impairment was extrapolated from PK studies with monotherapies (summarized as below).

QAB149

- Renal Impairment: per the labeling of ARCAPTA NEOHALER, “*Due to the very low contribution of the urinary pathway to total body elimination, a study in renally impaired subjects was not performed.*”
- Hepatic Impairment: per the labeling of ARCAPTA NEOHALER, “*Patients with*

mild and moderate hepatic impairment showed no relevant changes in Cmax or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatically impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.”

NVA237

- Renal Impairment: following a single NVA237 inhalation 100 mcg, the AUClast of glycopyrronium in patients with mild, moderate, server renal impairment (RI) and end stage renal disease (ESRD) were 1.42, 1.02, 2.21, and 2.07 fold higher compared to health subjects, respectively. Cmax of glycopyrronium were similar or even lower in RI and ESRD patients compared to healthy subjects. Therefore, the recommended dose of NVA237 12.5 mcg BID can be used in patients with mild and moderate RI. However, for patients with server RI and ESRD, the recommended dose should be used with caution.
- Hepatic Impairment: The effects of hepatic impairment on the pharmacokinetics of glycopyrrolate were not studied. Glycopyrrolate is cleared predominantly from systemic circulation by renal excretion.

For further details refer to ARCAPTA NEOHALER labeling, the Clinical Pharmacology Reviews of NDA22383 (ARCAPTA NEOHALER, Indacaterol Inhalation Powder) by Drs. Sandra S. Sharp and Ying Fan dated 08/25/2009, 09/09/2009, and 02/15/2011, and the Clinical Pharmacology Review of NDA207923 (Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis) by Dr. Lei He.

The relevant information based on the studies submitted in this NDA is summarized below.

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Population PK models were developed to describe indacaterol and glycopyrronium systemic exposure in patients with COPD. Please see Pharmacometrics Review in Appendix 4.1 for additional details.

QAB149

Body weight, smoking status, age, and sex were identified as major covariates contributing to interpatient variability of indacaterol PK parameters. The estimate of between subject variability on CL/F in COPD patients is 37%.

NVA237

Body weight, smoking status, and baseline eGFR were identified as major factors contributing interpatient variability of glycopyrronium PK parameters. The estimate of between subject variability on CL/F in COPD patients is 42%.

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

No dose adjustments are needed for any of the aforementioned covariates.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

As stated in section 2.6.1.

2.6.2.3 Elderly

As stated in section 2.6.1.

2.6.2.4 Pediatric Patients

Inhaled QVA149 is indicated for the treatment of adult COPD patients only. Pharmacokinetic studies with inhaled QVA149 were not conducted in children (<18 years old).

2.6.2.5 Race/Ethnicity

No clinically relevant ethnic effect on the systemic exposure to indacaterol and glycopyrronium was observed.

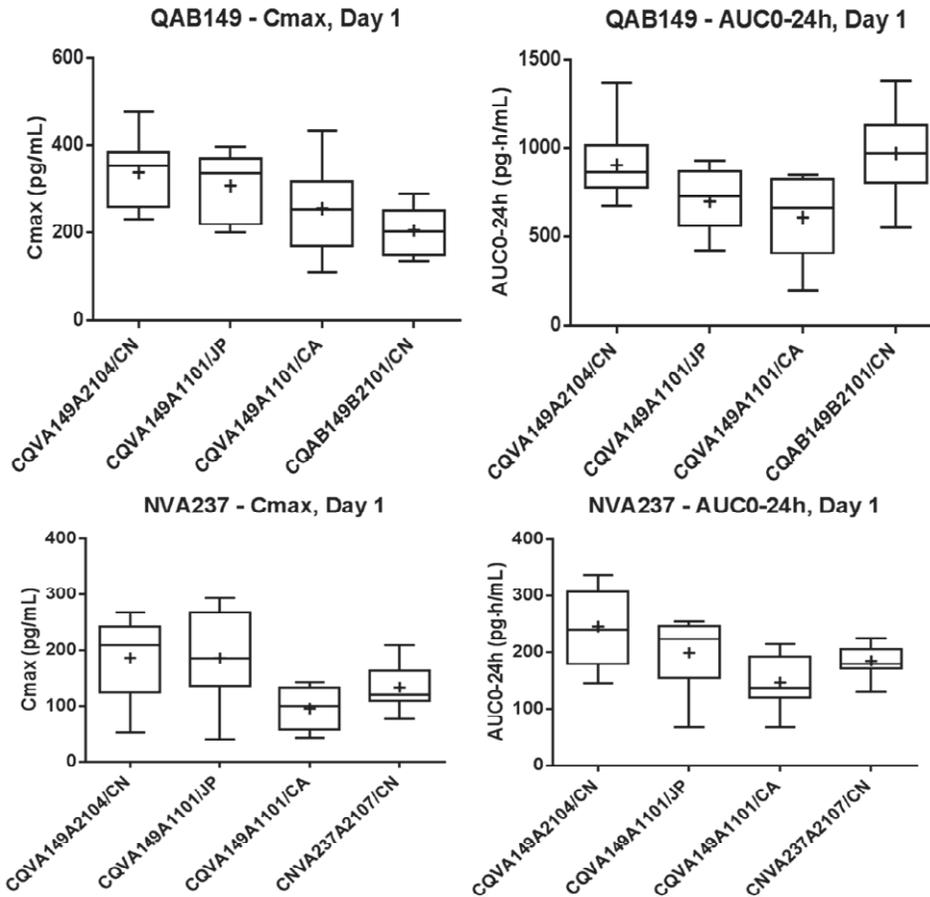
Population PK analysis

In population PK analysis including 480 Caucasians, 22 Blacks, and 47 Asians (46 Japanese):

- QAB149: there is no significant difference in indacaterol PK among races/ethnicities.
- NVA237: for patients with the same body weight, AUC_{0-24h} in Japanese and non-Japanese patients was similar; C_{max} in Japanese patients was estimated to be 76% higher than in non-Japanese because of a smaller volume of distribution of the central compartment, but was thought not clinically relevant.

Single dose PK in Chinese, Japanese, and Caucasian HVs

A cross-study comparison of indacaterol and glycopyrronium PK was performed based on single dose PK data from healthy Chinese subjects (Study QVA149A2104), and healthy Caucasian and Japanese subjects (Study QVA149A1101), and previous studies in healthy Chinese subjects (Studies QAB149B2101 and NVA237A2107). Results indicated that there is no clinically relevant ethnic difference in systemic exposure of indacaterol and glycopyrronium across healthy Chinese subjects, COPD Caucasian patients, and healthy Caucasian and Japanese subjects (Figure 10).



CN: Chinese; JP: Japanese; CA: Caucasian

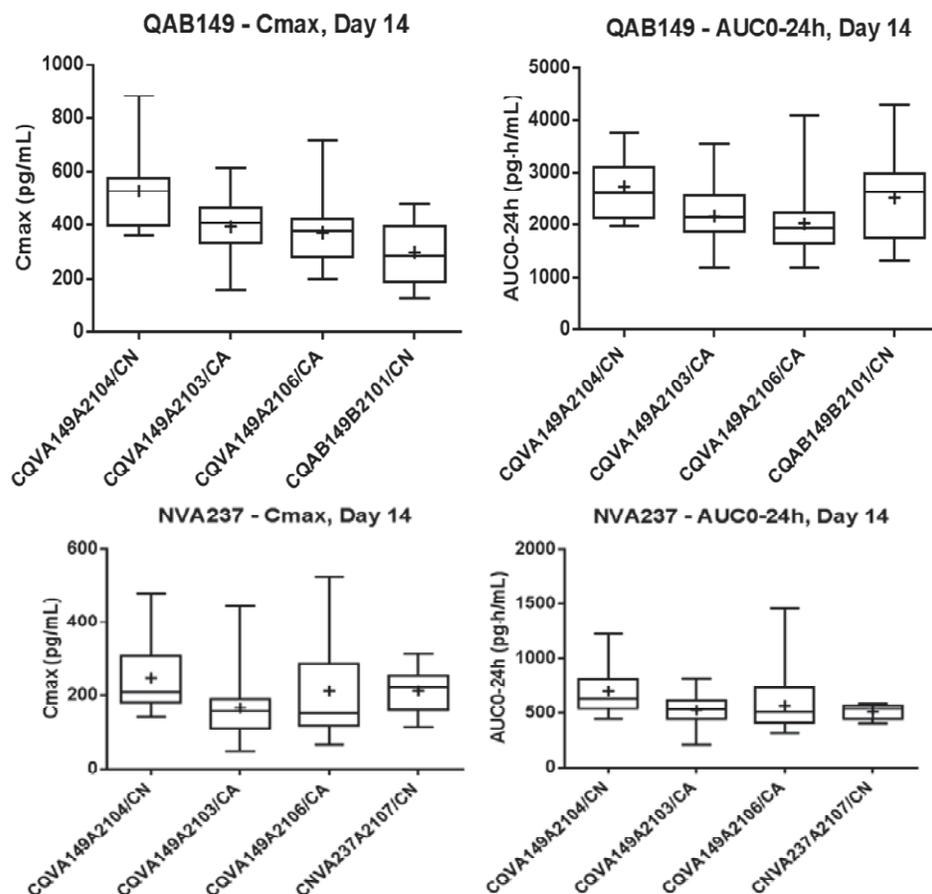
Solid lines in the box are median values, "+" are mean values; boxes depict 25th~75th percentile, Whiskers above and below the box indicate the maximum and minimum values.

Figure 10. Comparison of Cmax and AUC0-24h of indacaterol and glycopyrrolate in healthy Chinese subjects (QVA149A2104), healthy Caucasian and Japanese subjects (QVA149A1101) following QVA149 110/50 mcg, in healthy Chinese subjects following QAB149 150 mcg (QAB149B2101), and in healthy Chinese subjects following NVA237 50 mcg (NVA237A2107) via Concept 1 (Day 1)

(Source: Adapted from Figures 3-5, 3-6. Summary of Clinical Pharmacology)

Multiple dose PK at steady state in Chinese and Caucasian

A cross-study comparison of indacaterol and glycopyrrolate steady-state PK was performed based on PK data in healthy Chinese subjects (Study QVA149A2104), healthy Caucasian subjects (Study QVA149A2103 and QVA149A2106), as well as with PK data in healthy Chinese from previous studies conducted for the monotherapy components with matching doses (Studies QAB149B2101 and NVA237A2107). Results indicated that there is no clinically relevant ethnic difference in systemic exposure of indacaterol and glycopyrrolate across healthy Chinese subjects, COPD Caucasian patients, and healthy Caucasian and Japanese subjects (Figure 11).



CN: Chinese; CA: Caucasian

Solid lines in the box are median values, "+" are mean values; boxes depict 25th-75th percentile, Whiskers above and below the box indicate the maximum and minimum values.

Figure 11. Comparison of C_{max,ss} and AUC_{0-24h,ss} of indacaterol and glycopyrrolate in healthy Chinese subjects (QVA149A2104), healthy Caucasian subjects (QVA149A2103 and QVA149A2106) following QVA149 110/50 mcg QD, in healthy Chinese subjects following QAB149 150 mcg QD (QAB149B2101), and in healthy Chinese subjects following NVA237 50 mcg QD (NVA237A2107) via Concept 1 (Day 14)

(Source: Adapted from Figures 3-7, 3-8. Summary of Clinical Pharmacology)



(b) (4)

For details of Study QAB149B2101 and Study NVA237A2107, refer to the Clinical Pharmacology Reviews of NDA22383 by Drs. Sandra S. Sharp and Ying Fan dated 08/25/2009 and the Clinical Pharmacology Review of NDA207923 by Dr. Lei He.

2.6.2.6 Renal Impairment

No additional relevant studies were conducted for QVA149.

2.6.2.7 Hepatic Impairment

No additional relevant studies were conducted for QVA149.

2.6.3 Does genetic variation impact exposure and/or response?

No additional pharmacogenetic impact was assessed in this NDA. The relevant information of monotherapies as below could be extrapolated to QVA149.

For indacaterol, per the labeling of ARCAPTA NEOHALER, “*The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)7/(TA)7 genotype (low UGT1A1 expression; also referred to as *28) and the (TA)6, (TA)6 genotype. Steady-state AUC and C_{max} of indacaterol were 1.2-fold higher in the [(TA)7, (TA)7] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.*”

For glycopyrrolate, the pharmacogenetic impact was not assessed.

2.7 Extrinsic Factors

As stated above, for QVA149, the relevant information regarding extrinsic factors could be extrapolated from studies with monotherapies (summarized as below).

- For QAB149, per the labeling of ARCAPTA NEOHALER, “*Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil and ritonavir). The data suggest that systemic clearance is influenced by modulation of both P-gp and CYP3A4 activities and that the 1.9-fold AUC₀₋₂₄ increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. ARCAPTA NEOHALER was evaluated in clinical trials for up to one year at doses up to 600 mcg. No dose adjustment is warranted at the 75 mcg dose.*”
- For NVA237, co-administration of cimetidine (an OCT2 inhibitor) resulted in a modest increase in mean glycopyrronium AUC_{last} by 22% but similar C_{max}. Therefore, no dose adjustment is recommended when NVA237 is co-administered with cimetidine.

For further details refer to ARCAPTA NEOHALER labeling, the Clinical Pharmacology Reviews of NDA22383 (ARCAPTA NEOHALER, Indacaterol Inhalation Powder) by Drs. Sandra S. Sharp and Ying Fan dated 08/25/2009, 09/09/2009, and 02/15/2011, and the Clinical Pharmacology Review of NDA207923 (Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis) by Dr. Lei He.

The relevant information based on the studies submitted in this NDA is summarized below.

2.7.7 What are the drug-drug interactions?

The PK interaction between glycopyrronium and indacaterol was assessed in Study QVA149A2107. Following multiple BID administration of QVA149 27.5/12.5 mcg (x 2), indacaterol 27.5 mcg (x 2) alone, and glycopyrronium 12.5 mcg (x 2) alone, the steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrronium was

similar between the combination product and monotherapies, suggesting there is no PK interaction between the two components (Table 15).

Table 15. Comparison of glycopyrrolate and indacaterol PK parameters following BID administration of QVA149 and each drug inhaled alone

Compound	Parameter	GMR (90% CI)
Glycopyrrolate	C _{max,ss}	1.07 (0.97, 1.18)
	AUC _{0-12h,ss}	1.09 (1.05, 1.13)
Indacaterol	C _{max,ss}	0.97 (0.93, 1.02)
	AUC _{0-12h,ss}	0.95 (0.91, 0.99)

(Source: adapted from Tables 11-5 and 11-6, Study QVA149A2107 report)

2.7.8 Does the label specify co-administration of another drug?

The QVA149 label does not mention specific co-administration with other drugs.

2.7.9 What other co-medications are likely to be administered to the target population?

All COPD patients are likely to take other medications for treatment of COPD as listed under 2.2.4.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Indacaterol is a LABA. Co-administration with additional adrenergic drugs may potentiate the effect of indacaterol. Co-administration with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of indacaterol. Co-administration of LABA and diuretics may worsen the hypokalemia and electrocardiographic changes. Co-administration of beta-blockers may block the bronchodilatory effect and produce severe bronchospasm. Monoamine oxidase inhibitors, tricyclic antidepressants, and other known QTc prolonging drugs may potentiate effect of indacaterol on cardiovascular system.

Glycopyrrolate is a LAMA. Co-administration of anticholinergics may lead to an increase in anticholinergic adverse effects.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The sponsor did not provide BCS classification information for indacaterol and glycopyrrolate in this submission.

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The proposed to-be-marketed drug product is QVA149 27.5/12.5 mcg inhalation powder hard capsule administered via NEOHALER device. It was used in key studies of the

clinical development program, including the dose selection study (StudyQVA149A2210) and pivotal Phase 3 studies (Studies QVA149A2336, A2337, and A2340).

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food on the PK of QVA149 was not assessed. Since QVA149 is an inhaled drug product, food is not expected to have an impact on lung deposition.

2.8.4 Was the bioequivalence of the different strengths of the to-be-marketed formulation tested? If so were they bioequivalent or not?

Only one strength, QVA149 27.5/12.5 mcg, was proposed for the to-be-marketed product. No studies were conducted to test the bioequivalence of the different strengths.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Determinations of indacaterol and glycopyrronium in plasma were performed by using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

All submitted validation reports of analytical methods which were used for the determination of different analyte in human plasma and urine are summarized in Table 16.

Table 16. Validation reports of analytical methods used in QVA149 clinical trials

Analyte	Matrix	LLOQ	Validation Report	Clinical studies supported
NVA237	Plasma	1.5 pg/mL	R0900330C R0900330C-01	NVA237A2107 NVA237A2317 NVA237A2318 QVA149A2104 QVA149A2107 QVA149A2109 QVA149A2336 QVA149A2337
QAB149	plasma	5 pg/mL	R0800444D R0800444D-01	QVA149A2104 QVA149A2107 QVA149A2109 QVA149A2336 QVA149A2337
QAB149	Serum	10 pg/mL	R0800444	QAB149B2106
QAB149	plasma	10 pg/mL	R0800444A-01	QVA149A1101 QVA149A2103 QVA149A2105 QVA149A2106 QVA149A2303
QAB149	plasma	10 pg/mL	R0300366G R0300366G-01	QVA149A2101 QVA149A2203 QVA149A2204

M9	Plasma	50 pg/mL	R1100006-01	NVA237A2108
M9	Urine	50 pg/mL	R1100006C-01	NVA237A2108
Salmeterol	Plasma	2.5 pg/mL	1200379	QVA149A2105

(Source: adapted from Table 1-3 and Table 4-1of summary of biopharmaceutic studies)

NVA237

Validation report R0900330C (with amendment R0900330C 01) has been submitted to support the Glycopyrrolate Inhalation Powder application under NDA207923. For further details refer to the Clinical Pharmacology Review of NDA207923 by Dr. Lei He.

QAB149

Three analytical methods have been used for human plasma indacaterol measurement in relevant clinical studies. The validation reports of the three analytical methods are summarized in Table 17.

Table 17. Summary of analytical method validation reports for indacaterol quantification in human plasma

Report	Method description and performance	
R0800444D R0800444D-01	Title: Quantitative determination of QAB149 in human plasma by LC- MS/MS	
	LLOQ	5.0 pg/mL
	Calibration curve	5.0 -2000 pg/mL (ULOQ) Linear regression, weighting factor: $1/x^2$
	Matrix effect	Mean matrix factor: 1.09 (Range: 1.05-1.13) Precision $\leq 3.7\%$
	Recovery	72.6% (68.6-79.0%) Precision $\leq 7.7\%$
	Intra-day accuracy and precision	Mean bias $\leq 5.0\%$ (-2.0% at LLOQ) Precision $\leq 8.2\%$ (8.2% at LLOQ)
	Inter-day accuracy and precision	Mean bias $\leq 6.0\%$ (-6.0% at LLOQ) Precision $\leq 9.5\%$ (9.5% at LLOQ)
	Stability	<u>Post-preparative stability:</u> 15.0 pg/mL at 10°C for 98 hrs: mean bias of -6.7%, Precision of 10.9% 1600 pg/mL at 10°C for 98 hrs: mean bias of -3.1%, Precision of 1.9% <u>Freeze-thaw stability (5 cycles)</u> 15.0 pg/mL at -70 °C : mean bias 0%, Precision $\leq 7.1\%$ 1600 pg/mL at -70 °C : mean bias 5.6%, Precision $\leq 2.1\%$ <u>Stability in spiked human plasma</u> 15.0 pg/mL at RT for 20 hours: mean bias 3.3%, Precision 4.0% 15 pg/mL at -15 °C for 504 days: mean bias -9.8%, Precision 6.8% 15 pg/mL at -70 °C for 504 days: mean bias -9.8%, Precision 6.8%
R0800444A-01	Title: Validation of an LC-MS/MS method for the determination of QAB149 in human plasma	
	LLOQ	10.0 pg/mL
	Calibration curve	10.0-2000 pg/mL(ULOQ) Linear regression, weighting factor: $1/x^2$
	Matrix effect	Mean matrix factor: 0.80, 0.76, 0.78 Precision $\leq 8.0\%$
	Recovery	84.8% (83.3-87.6%) Precision $\leq 10.1\%$
	Intra-day accuracy and precision	Mean bias $\leq -3.8\%$ (-1.1% at LLOQ) Precision $\leq 14.1\%$ (14.1 % at LLOQ)

	precision	
	Inter-day accuracy and precision	Mean bias \leq -11.9% (-11.9% at LLOQ) Precision \leq 14.1% (14.1% at LLOQ)
	Dilutions	10-fold dilution
	Stability	<u>Post-preparative stability:</u> 30.0 pg/mL at 8°C for 118 hrs : mean bias -1.0 %, Precision 11.5% 1600 pg/mL at 8°C for 118 hrs : mean bias 1.9%, Precision 1.5% <u>Freeze-thaw stability (5 cycles)</u> 30.0 pg/mL at -15 °C : mean bias 9.5%, Precision \leq 6.7% 1600 pg/mL at -15 °C : mean bias 12.6%, Precision \leq 3.1% <u>Stability in spiked human plasma</u> 30.0 pg/mL at -15 °C for 391 days: mean bias -4.6%, Precision 4.1% 1600 pg/mL at -15 °C for 391 days: mean bias -3.9%, Precision 1.9%
R0300366G R0300366G-01	Quantitative determination of QAB149 in human plasma by LC-MS/MS	
	LLOQ	10.00 pg/mL
	Calibration curve	10.0-2000 pg/mL (ULOQ) Linear regression, weighting factor: 1/x
	Matrix effect	Mean matrix factor: 0.894 (0.865-0.917) Precision \leq 2.9%
	Recovery	77.7% (75.7-84.9%) Precision \leq 8.3%
	Intra-day accuracy and precision	Mean bias \leq -14.0% (14.0% at LLOQ) Precision \leq 5.9% (5.9% at LLOQ)
	Inter-day accuracy and precision	Mean bias \leq 9.0% (9.0% at LLOQ) Precision \leq 7.5% (7.5% at LLOQ)
	Dilutions	NA
	Stability	<u>Stability in spiked human plasma</u> 30.0 pg/mL at RT for 4 days: mean bias -5.7%, Precision 3.5% 1800 pg/mL at RT for 4 days: mean bias -1.1%, Precision 2.5% 30.0 pg/mL at -18 °C for 38 weeks: mean bias -10.3%, Precision 4.1% 1800 pg/mL at -18 °C for 38 weeks: mean bias -10.7%, Precision 4.3%

*RT: room temperature

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples. No metabolites were quantified because the metabolites of NVA237 and QAB149 are not active and associated with efficacy or safety.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

5 WARNINGS AND PRECAUTIONS

(b) (4)

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of indacaterol, a component of QVA149 NEOHALER, may be potentiated [see Warnings and Precautions (5.3, 5.6, 5.7, 5.11)].

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of beta2- adrenergic agonists such as indacaterol, a component of QVA149 NEOHALER [see Warnings and Precautions (5.11)].

7.3 Non-Potassium-Sparing Diuretics

The electrocardiographic (ECG) changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as indacaterol, a component of QVA149 NEOHALER, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of QVA149 NEOHALER with non-potassium-sparing diuretics.

7.4 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

Indacaterol, one of the components of QVA149 NEOHALER, as with other beta2-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or other drugs known to prolong the QTc interval because the action of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval may have an increased risk of ventricular arrhythmias.

7.5 Beta-Blockers

Beta-adrenergic receptor antagonists (beta-blockers) and QVA149 NEOHALER may interfere with the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

7.6 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of QVA149 NEOHALER with other anticholinergic-containing drugs as this may

lead to an increase in anticholinergic adverse effects [see Warnings and Precautions (5.8, 5.9), Adverse Reactions (6)].

7.7 Inhibitors of Cytochrome P450 3A4 and P-gp Efflux Transporter

Drug interaction studies with indacaterol, a component of QVA149 NEOHALER, were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil, and ritonavir). The data suggest that systemic clearance of indacaterol is influenced by modulation of both P-gp and CYP3A4 activities and that the 2-fold area under the curve (AUC) increase caused by the strong dual inhibitor ketoconazole reflects the impact of maximal combined inhibition. Indacaterol was evaluated in clinical trials for up to 1 year at doses up to 600 mcg. Inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses of indacaterol. Therefore, no dose adjustment is warranted at the recommended 27.5/15.6 mcg twice-daily dose for QVA149 NEOHALER when administered concomitantly with inhibitors of CYP3A4 and P-gp [see *Clinical Pharmacology* (12.3)].

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

QVA149 NEOHALER is not indicated for use in children. The safety and efficacy of QVA149 NEOHALER in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of QVA149 NEOHALER dosage in geriatric patients is warranted. QVA149 NEOHALER can be used at the recommended dose in elderly patients 75 years of age and older.

Of the total number of subjects in clinical studies of QVA149 NEOHALER, 45% were aged 65 and older, while 11% were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

Based on the pharmacokinetic characteristics of its monotherapy components, QVA149 NEOHALER can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73m²) or end-stage renal disease requiring dialysis, QVA149 NEOHALER should be used ^{(b) (4)} ~~if the expected benefit outweighs the potential risk since the systemic exposure to glycopyrrolate may be increased in this population~~ [see ^{(b) (4)} *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

Based on the pharmacokinetic characteristics of its monotherapy components, QVA149 NEOHALER can be used at the recommended dose in patients with mild to moderate hepatic impairment. Studies in subjects with severe hepatic impairment have not been performed [see *Clinical Pharmacology* (12.3)].

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

(b) (4)

Cardiovascular Electrophysiology (b) (4)

(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 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 Cmax 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 7.56, 9.83) at 30 minutes after dosing. (b) (4) [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.](#)

(b) (4)

12.3 Pharmacokinetics

Absorption

Following inhalation of QVA149 NEOHALER, the median time to reach peak plasma concentrations of indacaterol and glycopyrrolate was achieved rapidly at approximately 15 minutes and 5 minutes, respectively. (b) (4)

The steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrrolate is similar after the twice-daily inhalation of 2 (times 2) capsules of QVA149 NEOHALER 27.5 mcg/15.6 mcg as compared to the twice-daily inhalation of the monotherapy products indacaterol 27.5 mcg (times 2) alone or glycopyrrolate 15.6 mcg (times 2) alone respectively.

Indacaterol: Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-hour dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 mcg and 600 mcg.

Glycopyrrolate: Following repeated once-daily inhalation in patients with COPD, pharmacokinetic steady-state of glycopyrrolate was reached within 1 week of treatment. (b) (4)

With once-daily doses of 124.8 mcg and 249.6 mcg, steady-state exposure to glycopyrrolate (AUC over the dosing interval) was about 1.4- to 1.7-fold higher than after the first dose. (b) (4)

Distribution

Indacaterol: After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557 L indicating an extensive distribution. The in vitro human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Glycopyrrolate: After intravenous administration, the steady-state volume of distribution (V_{ss}) of glycopyrrolate was 83 L and the volume of distribution in the terminal phase (V_z) was 376 L. (b) (4) The in vitro human plasma protein binding of glycopyrrolate was 38% to 41% at concentrations of 1 to 10 ng/mL.

Metabolism

Indacaterol: In vitro investigations indicated that UGT1A1 is the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. In vitro investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for about one-third of total drug-related AUC over 24 hours. 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.

hours) and oral (2.8 hours) administration. (b) (4)

Drug Interactions

There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled glycopyrrolate and inhaled indacaterol based on steady-state exposure data.

No specific drug-drug interaction studies were conducted with QVA149 NEOHALER. Information on the potential for interactions for QVA149 NEOHALER is based on the potential for each of its 2 monotherapy components.

Indacaterol

Inhibitors of Cytochrome P450 3A4 and P-gp Efflux Transporter: Drug interaction studies were carried out using potent and specific inhibitors of CYP3A4 and P-gp (i.e., ketoconazole, erythromycin, verapamil and ritonavir). Coadministration of indacaterol 300 mcg (single dose) with verapamil (80 mg 3 times a day for 4 days) showed 2-fold increase in indacaterol AUC_{0-24h}, and 1.5-fold increase in indacaterol C_{max}. Coadministration of indacaterol inhalation powder 300 mcg (single dose) with erythromycin (400 mg 4 times a day for 7 days) showed a 1.4-fold increase in indacaterol AUC_{0-24h}, and 1.2-fold increase in indacaterol C_{max}. Coadministration of indacaterol inhalation powder 300 mcg (single dose) with ketoconazole (200 mg twice-daily for 7 days) caused a 1.9-fold increase in indacaterol AUC_{0-24h}, and 1.3-fold increase in indacaterol C_{max}. Coadministration of indacaterol 300 mcg (single dose) with ritonavir (300 mg twice-daily for 7.5 days) resulted in a 1.7-fold increase in indacaterol AUC_{0-24h} whereas indacaterol C_{max} was unaffected [see *Drug Interactions* (7.7)].

Glycopyrrolate

Cimetidine or Other Inhibitors of Organic Cationic Transport: In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of glycopyrrolate, increased total exposure (AUC) to glycopyrrolate by 22% and decreased renal clearance by 23%. (b) (4)

Special Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (40 to 85 years), body weight (45 to 120 kg), gender, smoking status, and baseline FEV₁ on systemic exposure of either indacaterol or glycopyrrolate following inhalation of QVA149 NEOHALER.

Similarly no relevant covariate effect (of age body weight, gender, smoking status, and baseline FEV₁) was observed following the inhalation of the 2 components indacaterol and glycopyrrolate separately.

Patients with Renal Impairment

(b) (4)

Indacaterol: Due to the very low contribution of the urinary pathway to total body elimination of indacaterol, a study in renally impaired subjects was not performed.

Glycopyrrolate: Renal impairment has an impact on the systemic exposure to glycopyrrolate. A moderate mean increase in total systemic exposure (AUC last) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease. (b) (4)

Patients with Hepatic Impairment

Based on the clinical pharmacokinetic characteristics of its monotherapy components, QVA149 NEOHALER can be used at the recommended dose in patients with mild and moderate hepatic impairment. QVA149 NEOHALER has not been evaluated in subjects with severe hepatic impairment.

Indacaterol: Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Glycopyrrolate: Clinical studies in patients with hepatic impairment have not been conducted.

Glycopyrrolate is cleared predominantly from the systemic circulation by renal excretion.

(b) (4)

Ethnicity

There was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, and Japanese subjects) on the systemic exposure to indacaterol and glycopyrrolate following inhalation of QVA149 NEOHALER.

Similarly, no relevant ethnic effect was observed following the inhalation of the 2 components indacaterol and glycopyrrolate separately.

12.5 Pharmacogenomics

Indacaterol: The pharmacokinetics of indacaterol were prospectively investigated in subjects with the UGT1A1 (TA)₇/(TA)₇ genotype (low UGT1A1 expression; also referred to as *28) and the (TA)₆, (TA)₆ genotype. Steady-state AUC and C_{max} of indacaterol were 1.2-fold higher in the [(TA)₇, (TA)₇] genotype, suggesting no relevant effect of UGT1A1 genotype of indacaterol exposure.

Glycopyrrolate: The effects of pharmacogenomic variants on the pharmacokinetics of glycopyrrolate have not been investigated.

4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	207930
Brand Name	UTIBRON NEOHALER
Drug Components	Indacaterol/Glycopyrrolate
Proposed dosing	Indacaterol 27.5 mcg/Glycopyrrolate 15.6 mcg, (equivalent to Indacaterol 27.5 mcg/ Glycopyrronium 12.5 mcg), administered via Neohaler device, BID
Pharmacometrics Reviewers	Lei He, Ph.D. Dinko Rekid, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Sponsor	Novartis

SUMMARY OF FINDINGS

The purpose of this review is to address the following key question.

Are there any covariates that influence the systemic exposure of indacaterol and glycopyrronium?

Indacaterol: Body weight, smoking status, age, and sex were identified as major covariates contributing to interpatient variability of indacaterol PK parameters (CL/F, Vc/F, Q/F and Vp/F). However, the small magnitude of covariate effects is not considered to be clinically relevant.

Glycopyrronium: Body weight, smoking status, and baseline eGFR were identified as major factors contributing interpatient variability of glycopyrronium PK parameters (CL/F, Vc/F, Q/F and Vp/F). Japanese ethnicity was identified as significant covariate on Vc/F. However, the small magnitude of covariate effects is not considered to be clinically relevant. Sex, age, and FEV1 on CL/F were not statistically significant covariates.

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

Absorption

Following inhalation of QVA149 NEOHALER, the median time to reach peak plasma concentrations of indacaterol and glycopyrrolate was achieved rapidly at approximately 15 minutes and 5 minutes, respectively. (b) (4)

The steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrrolate is similar after the twice-daily inhalation of 2 (times 2) capsules of QVA149 NEOHALER 27.5 mcg/15.6 mcg as compared to the twice-daily inhalation of the monotherapy products indacaterol 27.5 mcg (times 2) alone or glycopyrrolate 15.6 mcg (times 2) alone respectively.

Indacaterol: Indacaterol serum concentrations increased with repeated once-daily administration. Steady-state was achieved within 12 to 15 days. The mean accumulation ratio of indacaterol, i.e., AUC over the 24-hour dosing interval on Day 14 or Day 15 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 mcg and 600 mcg.

Glycopyrrolate: Following repeated once-daily inhalation in patients with COPD, pharmacokinetic steady-state of glycopyrrolate was reached within 1 week of treatment. (b) (4)

With once-daily doses of 124.8 mcg and 249.6 mcg, steady-state exposure to glycopyrrolate (AUC over the dosing interval) was about 1.4- to 1.7-fold higher than after the first dose. (b) (4)

Distribution

Indacaterol: After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557 L indicating an extensive distribution. The in vitro human serum and plasma protein binding was 94.1 to 95.3% and 95.1 to 96.2%, respectively.

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The in vitro human plasma protein binding of glycopyrrolate was 38% to 41% at concentrations of 1 to 10 ng/mL.

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After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) study, unchanged indacaterol was the main component in serum, accounting for

in the range of 17.4 L/h and 24.4 L/h. Active tubular secretion contributes to the renal elimination of glycopyrrolate. Up to 20% of the dose was found in urine as parent drug.

Glycopyrrolate plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life of glycopyrrolate was much longer after inhalation (33 to (b) (4) hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. (b) (4)

Drug Interactions

There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled glycopyrrolate and inhaled indacaterol based on steady-state exposure data.

No specific drug-drug interaction studies were conducted with QVA149 NEOHALER. Information on the potential for interactions for QVA149 NEOHALER is based on the potential for each of its 2 monotherapy components.

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Special Populations

Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (40 to 85 years), body weight (45 to 120 kg), gender, smoking status, and baseline FEV1 on systemic exposure of either indacaterol or glycopyrrolate following inhalation of QVA149 NEOHALER.

Similarly no relevant covariate effect (of age, body weight, gender, smoking status, and baseline FEV1) was observed following the inhalation of the 2 components indacaterol and glycopyrrolate separately.

Patients with Renal Impairment

(b) (4)

Indacaterol: Due to the very low contribution of the urinary pathway to total body elimination of indacaterol, a study in renally impaired subjects was not performed.

Glycopyrrolate: Renal impairment has an impact on the systemic exposure to glycopyrrolate. A moderate mean increase in total systemic exposure (AUC_{last}) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment and up to 2.2-fold in subjects with severe renal impairment and end stage renal

disease

(b) (4)

~~with a GFR greater than or equal to 30 mL/min/1.73 m²) glycopyrrolate can be used at the recommended dose.~~

Patients with Hepatic Impairment

Based on the clinical pharmacokinetic characteristics of its monotherapy components, QVA149 NEOHALER can be used at the recommended dose in patients with mild and moderate hepatic impairment. QVA149 NEOHALER has not been evaluated in subjects with severe hepatic impairment.

Indacaterol: Patients with mild and moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. Studies in subjects with severe hepatic impairment were not performed.

Glycopyrrolate: Clinical studies in patients with hepatic impairment have not been conducted.

Glycopyrrolate is cleared predominantly from the systemic circulation by renal excretion.

(b) (4)

Ethnicity

There was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, and Japanese subjects) on the systemic exposure to indacaterol and glycopyrrolate following inhalation of QVA149 NEOHALER.

Similarly, no relevant ethnic effect was observed following the inhalation of the 2 components indacaterol and glycopyrrolate separately.

SUMMARY OF SUBMISSION

Novartis has submitted NDA 207930 seeking the marketing approval for Indacaterol/ Glycopyrrolate Inhalation Powder (UTIBRON NEOHALER, a fixed-dose combination product of indacaterol and glycopyrrolate), which 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 dosing regimen is twice-daily inhalation of the contents of one 27.5/12.5 mcg UTIBRON capsule using the NEOHALER inhaler. The Sponsor supports NDA207930 submission with 11 clinical pharmacology studies.

The sponsor has also submitted NDA207923 at the same time as this NDA seeking the marketing approval for Glycopyrrolate Inhalation Powder (SEEBRI NEOHALER) for the same indication with 16 clinical pharmacology studies. The proposed dosing regimen is twice-daily inhalation of the contents of one 12.5 mcg SEEBRI capsule using the NEOHALER inhaler. Since glycopyrrolate is one of the individual components of Indacaterol/Glycopyrrolate Inhalation Powder, some studies were used to support both NDA207923 and NDA207930.

To date, several indacaterol and glycopyrrolate drug products have been approved in the United States:

ARCAPTA NEOHALER (Indacaterol Inhalation Powder, Novartis) was approved on 07/01/2011 under NDA022383 for the same indication as proposed for Indacaterol/ Glycopyrrolate Inhalation Powder and Glycopyrrolate Inhalation Powder. The recommended dosage of ARCAPTA NEOHALER is the once-daily (QD) inhalation of the contents of one 75 mcg ARCAPTA capsule using the NEOHALER inhaler.

Glycopyrrolate has been in clinical use for indications other than COPD for over 40 years and has been approved in more than 70 countries, including the United States.

A total of two population PK study reports were submitted in this NDA (Table 1). ^{(b) (4)}

 only Report [PopPK QVA149 27.5/12.5 mcg BID] was summarized in section 4.1.1.

Table 1. Summary of population PK study reports submitted in NDA207930

Report ID	Study Title	Data Source
CQVA149A2303-population-pk	Population Pharmacokinetics Modeling and Covariate Analysis of CQVA149A2303	CQVA149A2303 (110/50 QD)
PopPK QVA149 27.5/12.5 mcg BID	Population pharmacokinetics of QVA149 in COPD patients	CQVA149A2303 (110/50 QD) CQVA149A2336 (27.5/12.5 BID) CQVA149A2337 (27.5/12.5 BID)

4.1.1 Population pharmacokinetics of QVA149 in COPD patients

This section summarizes the population pharmacokinetic analysis conducted by the sponsor and main conclusions reached from this analysis.

Objectives

- To describe the population pharmacokinetics of indacaterol and glycopyrronium given as monotherapies or in a fixed-dose combination (FDC, QVA149 27.5/12.5 mcg), following multiple doses administered BID and to compare it to QVA149 110/50 mcg QD from the supportive program.
- To compare the dose-exposure relationship between QVA149 27.5/12.5 mcg and the monotherapy components (QAB149 27.5 mcg, NVA237 12.5 mcg) following a BID dosing regimen.
- To determine the effect of covariates on the PK of indacaterol and glycopyrronium.

Software

The PK model was constructed using the nonlinear mixed effect (NLME) modeling approach and was implemented in Monolix 4.3.2 (Lixoft, Paris, France).

Data Source

Data from 3 Phase 3 clinical studies in moderate-to severe COPD patients were pooled in the QVA149 population PK analysis: Studies A2336 and A2237 investigated the FDC QVA149 27.5/12.5 mcg BID and the monotherapy components QAB149 27.5 mcg BID and NVA237 12.5 mcg BID; Study A2303 investigated the FDC QVA149 110/50 mcg QD, and the monotherapy components QAB149 150 mcg QD and NVA237 50 mcg QD (Table 2).

Table 2. Studies and evaluable PK data included in the analysis

Study	Compound	Doses (μ g)	Regimen	Lower limit of quantification (LLOQ)
A2303	QVA149 (QAB149 / NVA237)	110/50	o.d.	10 pg/mL / 3 pg/mL
	QAB149	150	o.d.	10 pg/mL
	NVA237	50	o.d.	3 pg/mL
A2336, A2337*	QVA149 (QAB149 / NVA237)	27.5/12.5	b.i.d.	5 pg/mL / 1.5 pg/mL
	QAB149	27.5	b.i.d.	5 pg/mL
	NVA237	12.5	b.i.d.	1.5 pg/mL

*studies A2336 and A2337 had identical study designs.

(Source: Table 3-1, Population pharmacokinetics of QVA149 in COPD patients modeling report)

Population PK Model Development

One population PK model for each compound was developed. Each model combined PK data from both monotherapy components and fixed-dose combination arms of all three studies.

Structural Model

One- and two-compartment disposition models with first-order absorption or bolus administration were considered for indacaterol and glycopyrronium. The disposition kinetics was modeled using a parameterization involving apparent total clearance (CL/F), apparent central volume (Vc/F), apparent inter-compartmental clearance (Q/F), and apparent peripheral volume (Vp/F). A first-order absorption rate constant (Ka) was used to characterize the rate of the absorption process for indacaterol. Effect of FDC on the bioavailability of indacaterol and glycopyrronium was tested for inclusion into the base model. The first PK sample in studies included into the analysis was taken 5 minutes after the inhalation when the glycopyrronium plasma concentrations were already at Cmax. Thus, it was not possible to estimate the absorption rate and the absorption of glycopyrronium was described as an instantaneous bolus.

The dose-exposure relationships of indacaterol and glycopyrronium between QVA149 110/50 mcg and QVA149 27.5/12.5 mcg were indirectly evaluated by assessing differences between studies. Study effects were tested on bioavailability, Vc/F and CL/F, and were included on relative bioavailability for indacaterol and on Vc/F for glycopyrronium.

Between-subject variability (BSV) in pharmacokinetic parameters was modeled using multiplicative exponential model and residual variability was modeled using a proportional error model.

Covariate Model Development

Besides the inclusion of FDC effect on the relative bioavailability and differences in dose-exposure relationships in the structural model, the effect of the body weight on CL/F, Vc/F, Q/F and Vp/F for both indacaterol and glycopyrronium was also included in the base model with fixed power coefficients. The impact of other candidate covariates, including age, sex, race, baseline FEV1, smoking status, and eGFR was explored in a full covariate modeling approach as described below.

- Step 1. Include simultaneously all predefined covariates.
- Step 2. Remove non-significant covariates at the significance level $p < 0.01$ in the Wald test and refit the data.
- Step 3. Test remaining covariates for clinical relevance.

Final PK Model Evaluation

Model adequacy was primarily evaluated based on visual inspection of different diagnostic plots and precision of the parameter estimates. Predictive performance of the models was also assessed by the normalized prediction distribution errors (NPDE) and a visual predictive check VPC. These diagnostic plots were also stratified by study and day to ensure adequacy of the fit across these design factors.

Results

A total of 3468 PK samples of indacaterol and 3504 PK samples of glycopyrronium were used for model building (Table 3).

Table 3. PK data included into the analysis by study and treatment

Study	Treatment	Number of patients	Number of PK observations
A2303	NVA237 monotherapy	62	594
	QAB149 monotherapy	61	609
	NVA237 in QVA149	67	638
	QAB149 in QVA149	67	652
A2336	NVA237 monotherapy	61	558
	QAB149 monotherapy	56	506
	NVA237 in QVA149	59	533
	QAB149 in QVA149	59	534
A2337	NVA237 monotherapy	64	596
	QAB149 monotherapy	65	581
	NVA237 in QVA149	61	585
	QAB149 in QVA149	61	586
TOTAL	NVA237	374	3504
	QAB149	369	3468
	Both compounds	556	

Source: ./Results/QVA149_table_records_bytrt.csv; ./Scripts/QVA149_01_graphexp.R.

(Source: Table 5-1, Population pharmacokinetics of QVA149 in COPD patients modeling report)

Final model for indacaterol

The final model for indacaterol was a two-compartment disposition model with first-order absorption and first-order elimination. FDC effect was estimated on relative bioavailability in study A2303 and study effect on Vc/F for studies A2336 and A2337 relative to A2303. BSV was included on CL/F, Vc/F, Q/F, Vp/F and Ka. Between-occasion variability was not included. A proportional error model was used to describe the residual variability. Covariates included in the final model were: body weight on CL/F, Vc/F, Q/F and Vp/F, smoking status (current smoker versus ex-smoker) on CL/F, age on CL/F and sex on CL/F. Estimated parameters of the final model were shown in Table 4. Goodness of fit plots showed an adequate fit of the model (Figures 1-4).

Table 4. Parameter estimates for the final population PK model of indacaterol

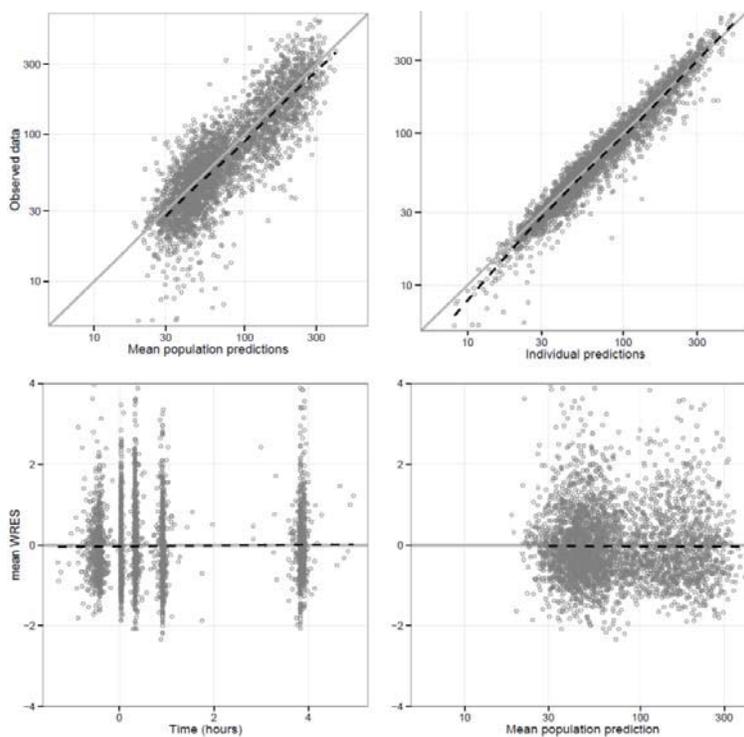
Parameter	Estimate (%RSE)	Shrinkage (%)
Structural parameters		
CL/F (L/h)	46.8 (3%)	
Vc/F (L)	918 (5%)	
Q/F (L/h)	259 (6%)	
Vp/F (L)	12000 (6%)	
Ka (1/h)	10.8 (6%)	
Relative bioavailability, F	1 (fixed)	
FDC effect on F in A2303	0.12 (35%)	
Study effect on Vc/F in A2336	0.34 (21%)	
Study effect on Vc/F in A2337	0.38 (18%)	
Between-subject variability		
BSV on CL/F	0.37 (4%)	10%
BSV on Vc/F	0.46 (5%)	33%
BSV on Q/F	0.5 (11%)	76%
BSV on Vp/F	0.86 (6%)	50%
BSV on Ka	0.73 (8%)	55%
BSV on F	0 (fixed)	
Corr(CL/F, Vc/F)	0.42 (15%)	
Covariate effects		
WT on CL/F, Q/F	0.75 (fixed)	
WT on Vc/F, Vp/F	1 (fixed)	
AGE on CL/F	-0.47 (34%)	
SEX on CL/F	-0.19 (23%)	
SMH on CL/F	0.18 (24%)	
Residual variability		
Proportional error (σ_{prop}), %	19% (2%)	

%RSE: relative standard error expressed as percentage, provided by Monolix;

Source: ./Models/FIT_06/QVA149_project/QAB149_table_par_FIT_06.csv;

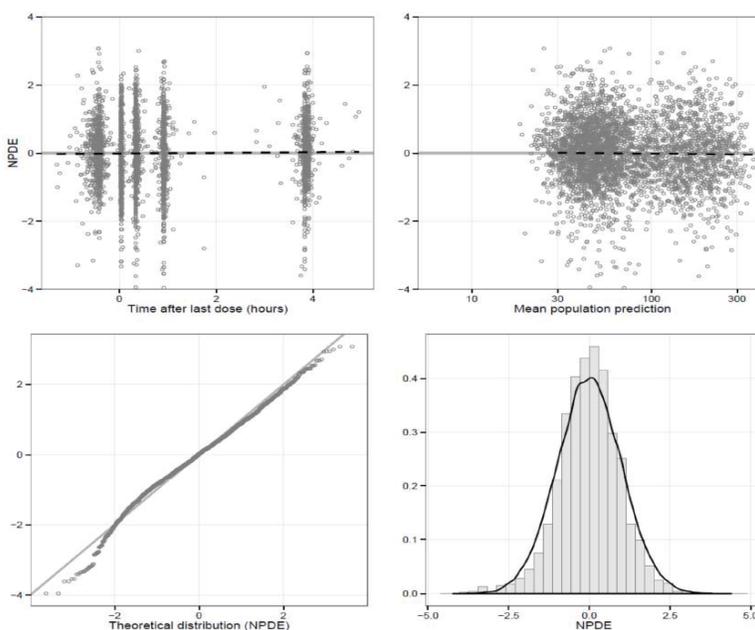
./Scripts/QVA149_032_PK_modevals.R.

(Source Table 5-9, Population pharmacokinetics of QVA149 in COPD patients modeling report)



Units for observed data and for predictions are pg/mL; dash line represents a loess line;
 Source: ./Models/FIT_06/QVA149_project/QAB149_PK_modevals_FIT_06.pdf;
 ./Scripts/QVA149_032_PK_modevals.R

Figure 1. Goodness-of-fit diagnostics for population PK model of indacaterol
 (Source: Figure 5-7, Population pharmacokinetics of QVA149 in COPD patients modeling report)



Units for predictions are pg/mL; dash line represents a loess line;
 top: NPDE versus time after last dose and mean population prediction;
 bottom: qqplot (left) and histogram (right) of NPDE;
 Source: ./Models/FIT_06/QVA149_project/QAB149_PK_modevals_FIT_06.pdf;
 ./Scripts/QVA149_032_PK_modevals.R

Figure 2. NPDE diagnostics for population PK model of indacaterol
 (Source: Figure 5-8, Population pharmacokinetics of QVA149 in COPD patients modeling report)

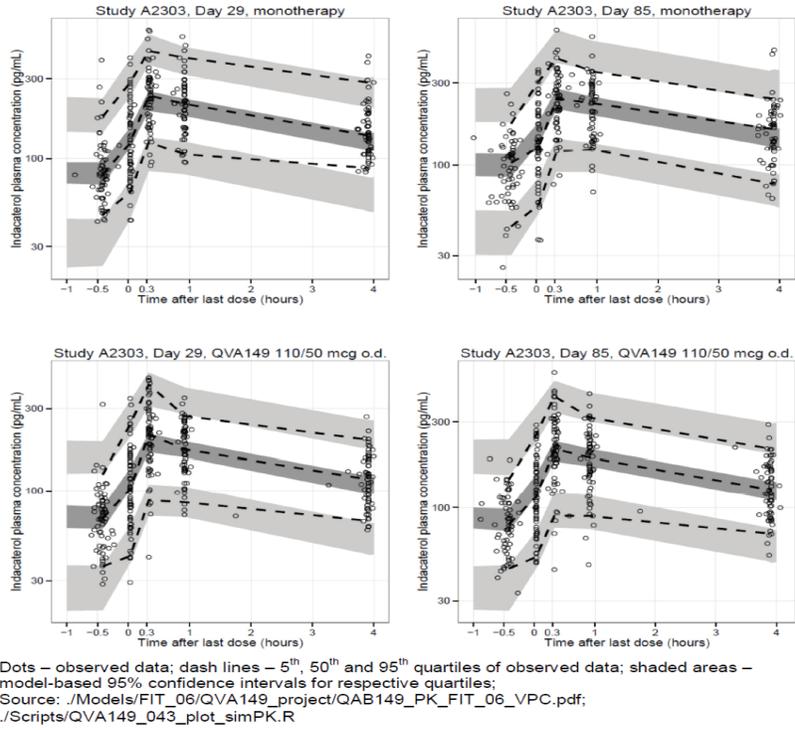


Figure 3. VPC for final population PK model of indacaterol for study A2303
 (Source: Figure 5-9, Population pharmacokinetics of QVA149 in COPD patients modeling report)

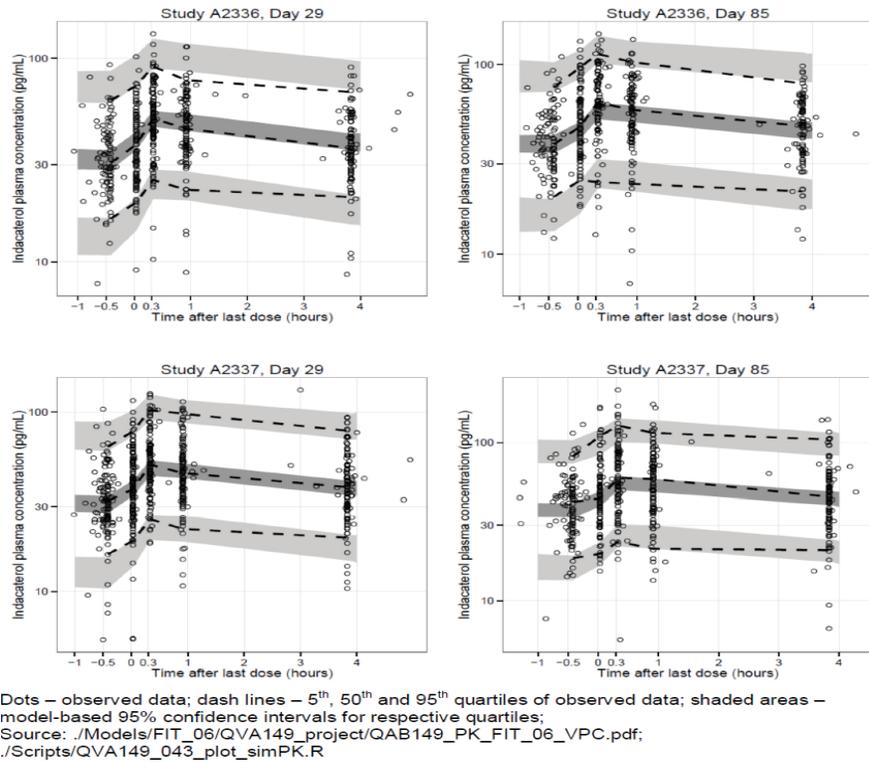


Figure 4. VPC for final population PK model of indacaterol for studies A2336, A2337
 (Source: Figure 5-10, Population pharmacokinetics of QVA149 in COPD patients modeling report)

Final model for glycopyrrolate

The final glycopyrronium PK model was a two-compartment disposition model with first-order elimination and bolus administration. BSV was included on CL/F and Vc/F. Between-occasion variability was not included. A proportional error model was used to describe the residual variability. Covariates included in the final model were: body weight on CL/F, Vc/F, Q/F and Vp/F, smoking status (current smoker versus ex-smoker) on CL/F, baseline eGFR on CL/F and Japanese ethnicity on Vc/F. Estimated parameters of the final model were shown in Table 5. Goodness of fit plots showed an adequate fit of the model (Figures 5-8).

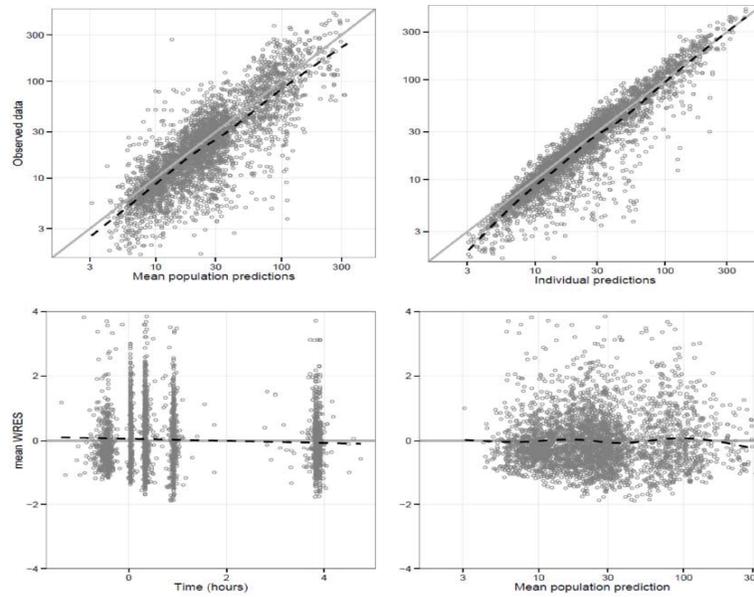
Table 5. Parameter estimates for the final population PK model of glycopyrronium

Parameter	Estimate (%RSE)	Shrinkage (%)
Structural parameters		
CL/F (L/h)	89.7 (3%)	
Vc/F (L)	676 (4%)	
Q/F (L/h)	268 (4%)	
Vp/F (L)	1300 (5%)	
Between-subject variability		
BSV on CL/F	0.42 (4%)	5%
BSV on Vc/F	0.68 (4%)	16%
Corr(CL/F, Vc/F)	0.33 (16%)	
Covariate effects		
WT on CL/F, Q/F	0.75 (fixed)	
WT on Vc/F, Vp/F	1 (fixed)	
SMH on CL/F	0.18 (24%)	
GFR on CL/F	0.55 (17%)	
RACE on Vc/F	-0.69 (19%)	
Residual variability		
Proportional error (σ_{prop}), %	31% (1%)	

%RSE: relative standard error expressed as percentage, provided by Monolix;

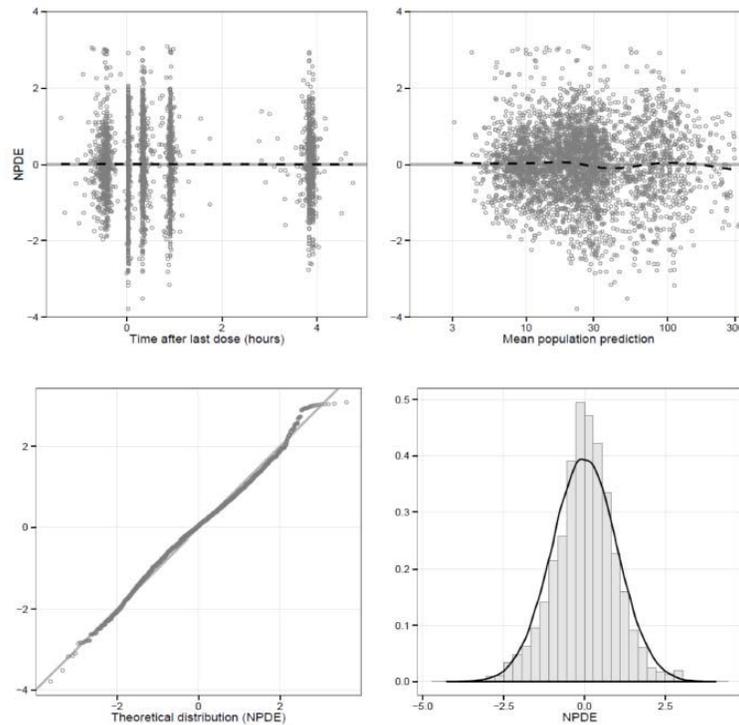
Source: ./Models/FIT_16/QVA149_project/pop_parameters.txt; NVA237_table_par_FIT_16.csv

(Source: Table 5-14, Population pharmacokinetics of QVA149 in COPD patients modeling report)



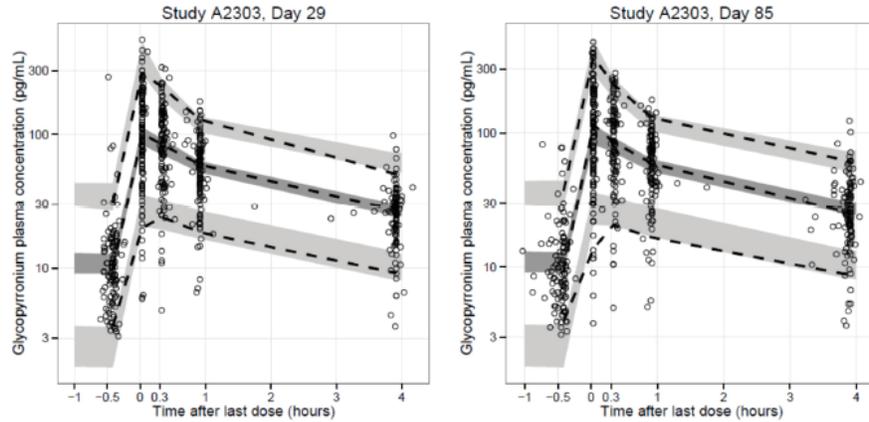
Units for observed data and for predictions are pg/mL; dash line represents a loess line;
 Source: ./Models/FIT_16/QVA149_project/NVA237_PK_modevals_FIT_16.pdf;
 ./Scripts/QVA149_032_PK_modevals.R

Figure 5. Goodness-of-fit diagnostics for final population PK model of glycopyrronium
 (Source: Figure 5-12, Population pharmacokinetics of QVA149 in COPD patients modeling report)



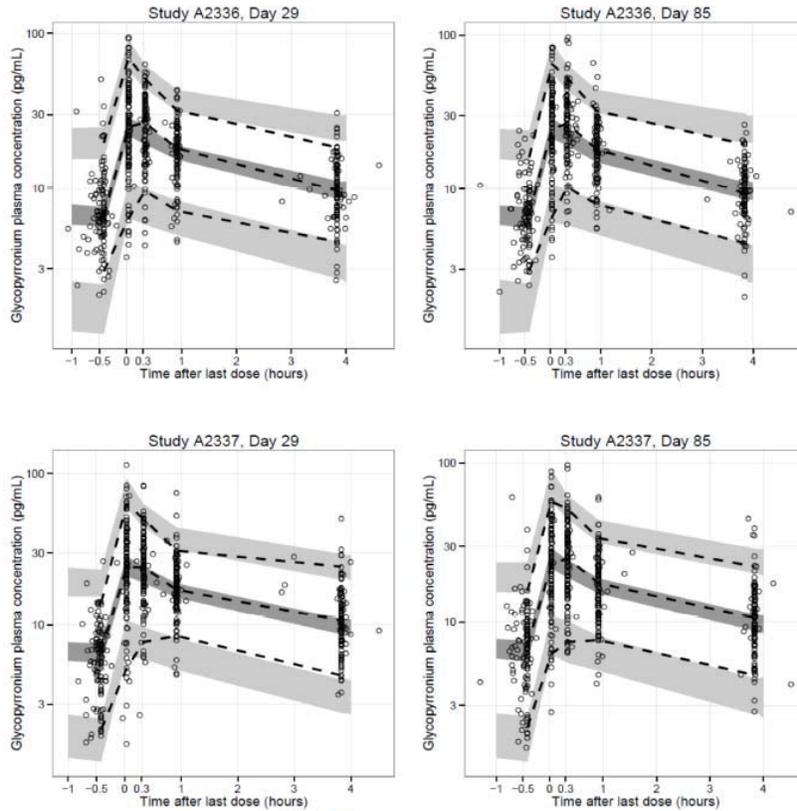
Units for predictions are pg/mL; dash line represents a loess line;
 top: NPDE versus time after last dose and mean population prediction;
 bottom: qqplot (left) and histogram (right) of NPDE;
 Source: ./Models/FIT_16/QVA149_project/NVA237_PK_modevals_FIT_16.pdf;
 ./Scripts/QVA149_032_PK_modevals.R

Figure 6. NPDE diagnostics for final population PK model of glycopyrronium
 (Source: Figure 5-13, Population pharmacokinetics of QVA149 in COPD patients modeling report)



Dots – observed data; dash lines – 5th, 50th and 95th quartiles of observed data; shaded areas – model-based 95% confidence intervals for respective quartiles;
 Source: /Models/FIT_16/QVA149_project/NVA237_PK_FIT_16_VPC.pdf;
 /Scripts/QVA149_043_plot_simPK.R

Figure 7. VPC for final population PK model of glycopyrronium for study A2303
 (Source: Figure 5-14, Population pharmacokinetics of QVA149 in COPD patients modeling report)



Dots – observed data; dash lines – 5th, 50th and 95th quartiles of observed data; shaded areas – model-based 95% confidence intervals for respective quartiles;
 Source: /Models/FIT_16/QVA149_project/NVA237_PK_FIT_16_VPC.pdf;
 /Scripts/QVA149_043_plot_simPK.R

Figure 8. VPC for final population PK model of glycopyrronium for studies A2336, A2337
 (Source: Figure 5-15, Population pharmacokinetics of QVA149 in COPD patients modeling report)

Conclusions

Indacaterol

- A two-compartment model with first-order absorption and first-order elimination described the systemic exposure of inhaled indacaterol in COPD population regardless of QD and BID regimen.
- Indacaterol PK is linear following inhalation of QVA149 27.5/12.5 mcg BID or QAB149 27.5 mcg BID.
- No difference was detected in dose-exposure relationship of indacaterol following the administration of QAB 149 27.5 mcg BID or QVA149 27.5/12.5 mcg BID.
- Body weight, smoking status, age, and sex were identified as major covariates contributing to interpatient variability of indacaterol PK parameters (CL/F, Vc/F, Q/F and Vp/F). However, the small magnitude of covariate effects is not considered to be clinically relevant.

Glycopyrrolate

- A two-compartment model with first-order absorption and first-order elimination described the systemic exposure of inhaled glycopyrronium in COPD population regardless of QD and BID regimen.
- Glycopyrronium PK is linear following inhalation of QVA149 27.5/12.5 mcg BID or NVA237 12.5 mcg BID.
- No difference was detected in dose-exposure relationship of indacaterol following the administration of NVA237 12.5 mcg BID or QVA149 27.5/12.5 mcg BID.
- Body weight, smoking status, and baseline eGFR were identified as major factors contributing interpatient variability of glycopyrronium PK parameters (CL/F, Vc/F, Q/F and Vp/F). However, the small magnitude of covariate effects is not considered to be clinically relevant.
- Japanese ethnicity was identified as significant covariate on Vc/F. Simulations indicated that compared to non-Japanese patients with the same body weight, the population mean AUC_{0-24h} in Japanese was similar, and C_{max} in Japanese patients was 76% higher because of a smaller volume of distribution of the central compartment. However, the small magnitude of covariate effects is not considered to be clinically relevant.
- Sex, age, and FEV1 on CL/F were not statistically significant covariates.

Reviewer's comments

The developed population PK models for indacaterol and glycopyrronium were repeated by the reviewer. Both models are adequate to describe the pharmacokinetics of indacaterol and glycopyrronium following inhalation of QAB149 27.5 mcg BID, NVA237 12.5 mcg BID, QVA149 27.5/12.5 mcg BID, and QVA 110/50 mcg QD.

In both population PK models for glycopyrronium including data from 27 Japanese patients in NDA207923 (NVA237) and 46 Japanese patients in NDA207930 (QVA149), the AUC was similar between Japanese and non-Japanese patients. However, the C_{max} was estimated to be 19% and 76% higher in Japanese patients because of a smaller volume of distribution of the central compartment.

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

In-Vitro Studies

Summary of studies pertinent to PK using human biomaterials

No *in vitro* studies using human biomaterials were carried out with QVA149. A total of 6 reports of *in vitro* hepatic metabolisms and drug interaction studies using individual components were submitted in this NDA (see Section 2.1): 3 studies with NVA237 were reviewed in NDA207923 application by Dr. Lei He; the other 3 studies with QAB149 are summarized in the table as below. In brief, QAB149 (up to 10 μM) does not appear to inhibit OATP1B3, hOAT1, and hOAT3. At the therapeutic dose level, the potential of indacaterol to inhibit CYP2B6, CYP2A6, and OATP1B1 is negligible.

Table 1. Summary of QAB149 *in vitro* hepatic metabolisms and drug interaction studies using human biomaterials

Report	Study Title	Method	Results
DMPK R1100624	In vitro assessment of cytochrome P450 2A6 and 2B6 enzyme inhibition by QAB149	The potential of QAB149 to inhibit human CYP2B6 and CYP2A6 enzyme activity was assessed by testing the effect of increasing concentrations of QAB149 on the <i>in vitro</i> metabolism of the probe substrate coumarin (coumarin 7-hydroxylation) and bupropion (bupropion hydroxylation) using pooled human liver microsomes.	QAB149 showed inhibitory potential for CYP2B6 ($\text{IC}_{50} \sim 5 \mu\text{M}$) and very weak inhibition of CYP2A6 ($\text{IC}_{50} \sim 100 \mu\text{M}$) enzyme activity in human liver microsomes.
DMPK R1100625	Assessment of QAB149 as an inhibitor of human organic anion transporting polypeptides 1B1 (OATP1B1) and 1B3 (OATP1B3)	The potential inhibitory effect of QAB149 (up to 10 μM) or the positive control inhibitor, rifamycin SV (20 μM) on the hepatic OATP1B1 and OATP1B3 was examined using HEK293 cells. Transport activity was evaluated by comparing the extent of probe substrates accumulation in cells that express OATP1B1 or OATP1B3 compared to control cells.	QAB149 showed inhibitory potential for OATP1B1 with $\text{IC}_{50} \sim 8 \mu\text{M}$. QAB149 (up to 10 μM) did not appreciably inhibit the OATP1B3 transport activity.
DMPK R1100671	Assessment of QAB149 as an inhibitor of human organic anion transporters 1 and 3	The potential inhibitory effect of QAB149 (up to 10 μM) or the positive control inhibitor, probenecid (500 μM) on the hOAT1 and hOAT3 was examined using HEK293 cells. Transport activity was evaluated by comparing the extent of probe substrates accumulation in cells that express hOAT1 or hOAT3 compared to control cells.	QAB149 (up to 10 μM) does not appear to be an <i>in vitro</i> inhibitor of the transport activity of hOAT1 or hOAT3.

Intrinsic Factor

Study QVA149A1101

Title: A single center, randomized, double-blind, placebo-controlled, single-ascending-dose study to assess safety and tolerability in Japanese and Caucasian healthy subjects following QVA149 inhaled administration.

Objectives

Primary: To assess the safety and tolerability of single inhaled doses of QVA149 delivered by SDDPI in Japanese and Caucasian healthy subjects.

Secondary: To evaluate the PK of single inhaled doses of QVA149 delivered by SDDPI in Japanese and Caucasian healthy subjects.

Study Design and Treatment Schedule: This is a single center, randomized, double-blind, placebo-controlled, single-ascending dose study in healthy subjects. A total of 48 subjects (24 Japanese and 24 Caucasians) were enrolled into the study. Each subject participated in a screening period (Day -28 to Day -2), a baseline evaluation (Day -1), a treatment period (Day 1 to 9), followed by a Study Completion evaluation (Day 10). On the morning of Day 1, following a fast of at least 10 hours, subjects were dosed under fasted conditions as per randomization schedule. Subjects remained in a fasting condition for 4 hours postdose. Following a single dose of QVA149, PK assessments were made up to 96 hours after dosing. Safety assessments were made up to study completion scheduled on Day 10.

	Cohort 1	The decision to proceed to cohort 2 was made based on a safety verification in the Cohort 1	Cohort 2*
Japanese (N = 24)	QVA149 110/50 µg (N=8) or Placebo (N=4)		QVA149 220/100 µg (N=8) or Placebo (N=4)
Caucasians (N = 24)	QVA149 110/50 µg (N=8) or Placebo (N=4)		QVA149 220/100 µg (N=8) or Placebo (N=4)

* QVA149 220/100 µg was administered as two inhalations of QVA149 110/50 µg.

Figure 1. Study design

(Source: Figure 9-1, Study QVA149A1101 report)

Table 2. Test Product

Study drug/SDDPI	Lot number (Batch number)	Expiration date
QVA149 capsule (110/50 µg)	J09001 (X101 0408)	April 2010
QVA149 placebo	J09002 (X160 0207)	February 2010
SDDPI	J09003 (B01427011001)	March 2010

(Source: Table 9-1, Study QVA149A1101 report)

PK Sampling Schedule

QVA149: Blood samples will be collected are presdose, and 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 h postdose.

NVA237: Blood samples will be collected are presdose, and 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 h postdose.

Results

The mean plasma concentration-time profiles and PK parameters for QAB149 and NVA237 are shown Figure 2 and Table 3. The comparison of QAB and NVA237 PK parameters between Japanese and Caucasians are shown in Table 4.

QAB149: Following inhalation of QVA149 110/50 mcg and 220/100 mcg, Cmax can be reached at 15 min (Tmax) in all treatments and plasma concentrations decreased rapidly thereafter. Following QVA149 110/50 mcg inhalation, QAB149 Cmax and AUC0-24h were slightly higher in Japanese subjects, while AUClast was similar between these two ethnicities (Notes that the plasma concentrations of QAB149 were above the LLOQ between 12 and 48 hours in the Japanese and between 8 and 96 hours in the Caucasians). Following QVA149 inhalation 220/100 mcg, Cmax, AUC0-24h, and AUClast were slightly higher in Japanese compared to Caucasians (Note that plasma concentrations of QAB149 were above the LLOQ until 48 and 24 hours in all Japanese and Caucasian subjects, respectively).

NVA237: Following inhalation of QVA149 110/50 mcg and 220/100 mcg, Cmax can be reached at 5 min (Tmax) in all treatments and plasma concentrations decreased rapidly thereafter. Following QVA149 110/50 mcg inhalation, NVA237 Cmax was slightly higher in Japanese subjects (Notes that the plasma concentrations of NVA237 were above the LLOQ until 8 hours in the Japanese and Caucasians). Following QVA149 inhalation 220/100 mcg, Cmax, AUC0-24h, and AUClast were slightly higher in Japanese compared to and 24 hours in Japanese and Caucasians.).

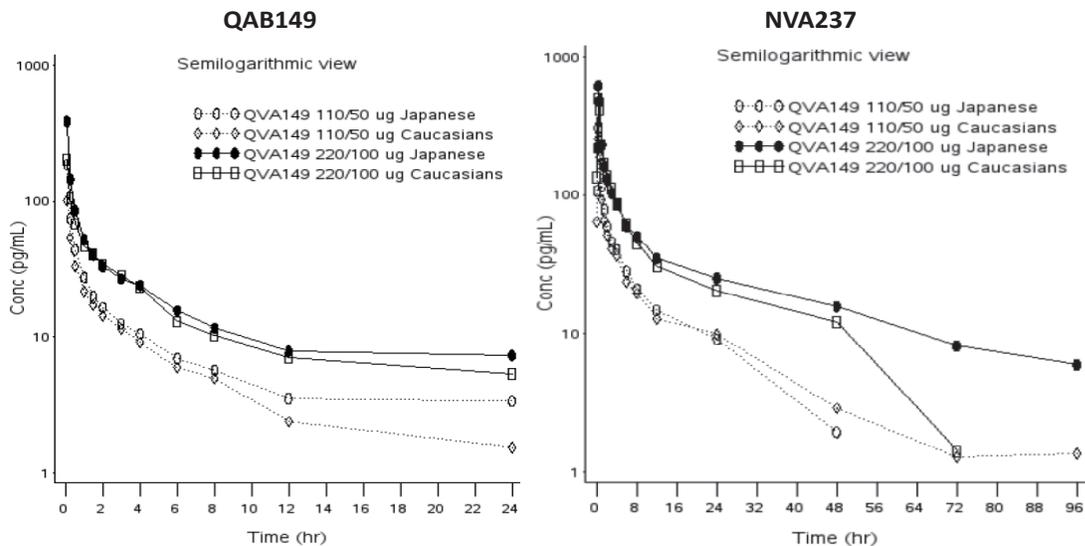


Figure 2. Arithmetic mean plasma concentration-time profiles of QAB149 and NVA237
(Adapted form Figures 11-1 and 11-2, Study QVA149A1101 report)

Table 3. Summary of primary PK parameters of QAB149 and NVA237

Analyte and Treatment	Ethnicity	AUClast	AUC0-24h	Cmax	Tmax
		(pg·h/mL) N=8	(pg·h/mL) N=8	(pg/mL) N=8	(h) N=8
QAB149					
QVA149 110/50 µg	Japanese	731.4 (242.97) 33.22%	702.9 (177.06) 25.19%	308.9 (75.435) 24.42%	0.25 (0.25-0.25)
	Caucasians	747.5 (486.80) 65.13%	613.7 (234.05) 38.14%	256.6 (101.44) 39.53%	
QVA149 220/100 µg	Japanese	2440 (589.42) 24.16%	1565 (311.63) 19.91%	620.0 (157.94) 25.47%	0.25 (0.25-0.25)
	Caucasians	1861 (600.49) 32.27%	1451 (493.36) 34.01%	510.6 (149.15) 29.21%	
NVA237					
QVA149 110/50 µg	Japanese	196.2 (70.556) 35.97%	199.7 (65.641) 32.88%	186.3 (83.407) 44.77%	0.083 (0.083-0.083)
	Caucasians	139.0 (53.259) 38.32%	147.2 (48.016) 32.61%	101.4 (46.796) 46.17%	
QVA149 220/100 µg	Japanese	419.1 (106.29) 25.36%	419.1 (106.29) 25.36%	388.5 (166.08) 42.75%	0.083 (0.083-0.083)
	Caucasians	352.3 (88.614) 25.15%	352.3 (88.614) 25.15%	202.6 (106.19) 52.40%	

Source: Post-text table 14.2-1.2

AUClast, AUC0-24h, Cmax: Upper line, Arithmetic Mean (SD); Lower line, CV%

Tmax: Median (Range)

(Source: Table 11-2, Study QVA149A1101 report)

Table 4. QAB149 and NVA237 PK comparison between Japanese and Caucasians

Treatment	Analyte	Parameter (unit)	Geometric mean		Ratio (J/C)	90% CI
			Japanese	Caucasian		
QVA149 110/50 µg	QAB149	AUClast (pg·h/mL)	691.7	609.2	1.14	(0.57, 2.27)
		AUC0-24h (pg·h/mL)	681.8	559.2	1.22	(0.73, 2.05)
		Cmax (pg/mL)	299.9	237.9	1.26	(0.77, 2.07)
	NVA237	AUClast (pg·h/mL)	179.5	129.4	1.39	(0.80, 2.41)
		AUC0-24h (pg·h/mL)	185.6	139.5	1.33	(0.80, 2.21)
		Cmax (pg/mL)	162.9	91.6	1.78	(0.77, 4.11)
QVA149 220/100 µg	QAB149	AUClast (pg·h/mL)	2366.1	1766.4	1.34	(0.67, 2.68)
		AUC0-24h (pg·h/mL)	1534.0	1385.2	1.11	(0.66, 1.86)
		Cmax (pg/mL)	599.6	489.8	1.22	(0.75, 2.01)
	NVA237	AUClast (pg·h/mL)	408.4	342.5	1.19	(0.68, 2.08)
		AUC0-24h (pg·h/mL)	408.4	342.5	1.19	(0.72, 1.98)
		Cmax (pg/mL)	344.9	179.4	1.92	(0.83, 4.45)

Source: Post-text table 14.2-1.4

(Source: Table 11-3, Study QVA149A1101 report)

Conclusions

- Both QAB149 and NVA237 were systemically available shortly after the inhalation with median Tmax of 15 min for QAB149 and 5 min for NVA237 in Japanese and Caucasians.
- Following QVA149 inhalation at 110/50 mcg and 220/100 mcg, the systemic exposure of QAB149 and NVA237 are slightly higher in Japanese compared to Caucasians. However, it was not considered clinically relevant.

Phase 1 PK study in HV
Study CQVA149A2101

Title: An open label, single-center, randomized, single-dose, four-way crossover study to assess the pharmacokinetics of a single inhaled dose of indacaterol and NVA237 when administered alone, in free, or in fixed combination in healthy subjects

Objectives:

Primary: To evaluate the relative bioavailability of indacaterol and NVA237 after administration in a fixed dose combination (FDC) as QVA149 (1 x 300 mcg indacaterol and 1 x 100 mcg NVA237) relative to the administration of indacaterol 300 mcg and NVA237 100 mcg dry powder inhaler formulation alone in HVs

Secondary:

- To evaluate the relative bioavailability of indacaterol and NVA237 after administration in a free combination indacaterol and NVA237 dry powder inhaler formulation as a single dose relative to indacaterol 300 mcg and NVA237 100 mcg dry powder inhaler formulation alone
- To evaluate the relative bioavailability of QVA149 (1 x 300 mcg indacaterol and 1 x 100 mcg NVA237) dry powder inhaler formulation relative to a free combination of 1 x 300 mcg indacaterol and 1 x 100 mcg NVA237
- To assess the safety and tolerability

Study Design and Treatment Schedule: This was an open-label, single center, randomized four-way crossover study. Each subject was to participate in a screening period (day -21 to day -2), four baseline periods, four single-dose treatment periods, with a washout period of at least fourteen days between two consecutive dose administrations, and a study completion evaluation.

Study treatments (fasted condition) were of the following:

- **Treatment 1:** 1 x 300 mcg indacaterol inhalation
- **Treatment 2:** 1 x 100 mcg NVA237 inhalation
- **Treatment 3:** free combination of 1 x 300 mcg indacaterol and 1 x 100 mcg NVA237 inhalation (NVA237 was to be inhaled first and then indacaterol)
- **Treatment 4:** QVA149 (1 x 300 mcg indacaterol and 1 x 100 mcg NVA237) inhalation

Subjects received all four treatments after randomization to one of the four sequences (in a 1:1:1:1 ratio) as shown below.

Table 5. Treatment sequence

	Period 1	Period 2	Period 3	Period 4
Sequence A	Indacaterol	NVA237	Indacaterol + NVA237	QVA149
Sequence B	NVA237	QVA149	Indacaterol	Indacaterol + NVA237
Sequence C	Indacaterol + NVA237	Indacaterol	QVA149	NVA237
Sequence D	QVA149	Indacaterol + NVA237	NVA237	Indacaterol

(Source: Table 9-1, Study QVA149A2101 report)

Table 6. Test Product

Study Drugs	Batch #
QAV149 (indacaterol + NVA237) 300 mcg + 100 mcg capsules	X153 0307
QAB149 (indacaterol) 300 mcg capsules	X261GC
NVA237 (glycopyrrolate) 100 mcg capsules	X011 0107
Placebo capsules	X160 0207
Empty Concept1 inhaler devices	B17616011001

PK Sampling Schedule

PK blood collection for indacaterol: blood was collected at 0 (pre-dose), 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours post-dose.

PK blood collection for NVA237: blood was collected at 0 (pre-dose), 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose.

Results

A total of 28 subjects were enrolled and completed the study, except one subject withdraw after Period 2. The PK profiles, summary of PK parameters, and relative bioavailability of indacaterol and glycopyrrolate are shown in Figure 3 and Tables 7-11.

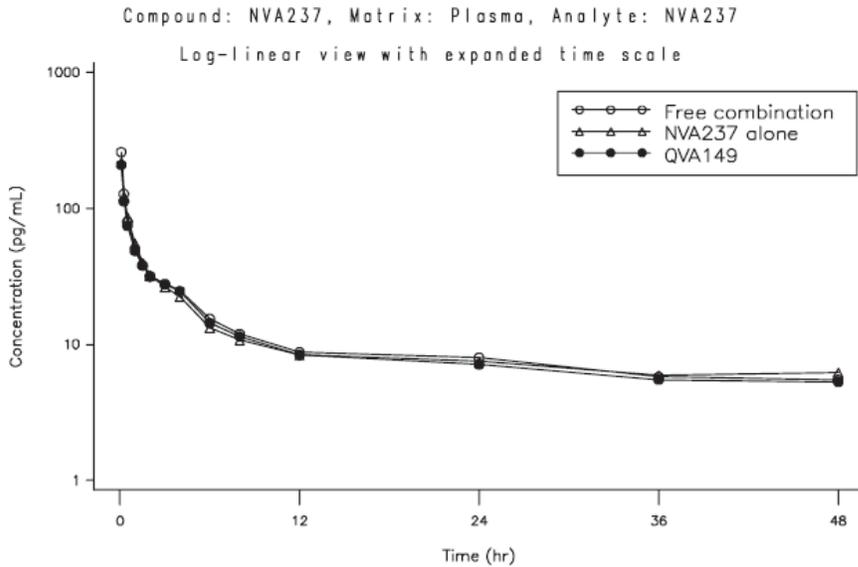
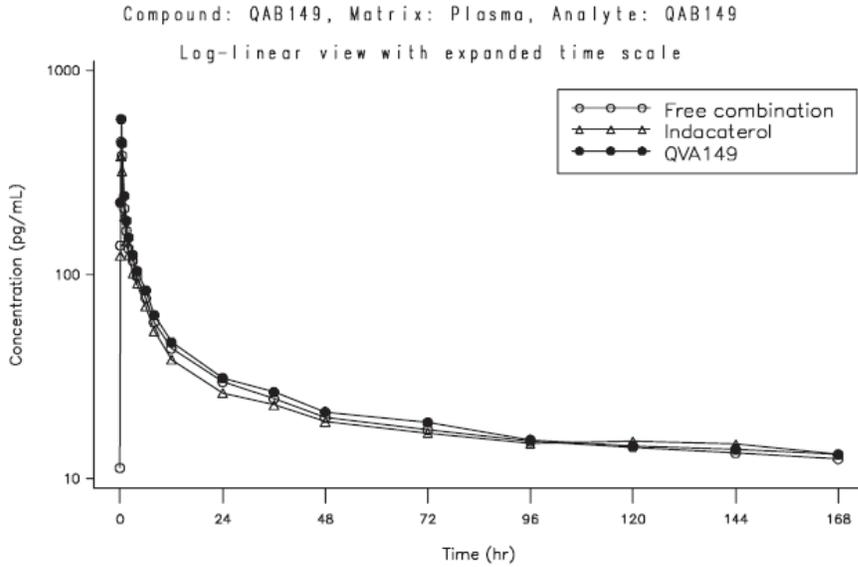


Figure 3. Geometric mean plasma concentration-time profiles of indacaterol (upper panel) and glycopyrronium (lower panel)

(Source: Figure 11-1, Study QVA149A2101 report)

Table 7. Summary of pharmacokinetic parameters of indacaterol

Parameter	Treatment		
	QVA149 (n=27)	Free combination (n=27)	Indacaterol alone (n=28)
AUC _{0-tlast} (h•pg/mL)	4149 (2357)	3783 (2273)	3417 (2267)
AUC _{0-24h} (h•pg/mL)	2028 (1052)	1826 (1013)	1642 (954)
C _{max} (pg/mL)	639 (307)	498 (260)	414 (194)
T _{max} (h) ¹⁾	0.25 (0.25-0.50)	0.25 (0.25-0.50)	0.25 (0.25-0.50)
t _{1/2} (h)	94.5 (45.8) ²⁾	93.7 (62.0) ³⁾	88.0 (38.4) ⁴⁾

¹⁾ Median (Range); ²⁾ n = 18; ³⁾ n = 19; ⁴⁾ n = 17

(Source: Table 1, Study QVA149A2101 report)

Table 8. Summary of pharmacokinetic parameters of NVA237

Parameter	Treatment		
	QVA149 (n=27)	Free combination (n=27)	NVA237 alone (n=28)
AUC _{0-tlast} (h•pg/mL)	504 (198)	563 (195)	532 (171)
AUC _{0-24h} (h•pg/mL)	407 (132)	430 (144)	409 (104)
C _{max} (pg/mL)	261 (207)	316 (202)	249 (121)
T _{max} (h) ¹⁾	0.08 (0.08-0.13)	0.08 (0.08-0.13)	0.08 (0.08-1.00)
t _½ (h)	40.0 (41.7) ²⁾	37.2 (11.7) ³⁾	33.4 (22.9) ⁴⁾

¹⁾ Median (Range); ²⁾ n = 13; ³⁾ n = 11; ⁴⁾ n = 9
(Source: Table 2, Study QVA149A2101 report)

Table 9. Relative bioavailability of indacaterol and NVA237 after administration of QVA149 relative to administration of each compound alone

Compound	Parameter (unit)	Ratio QVA149/Alone [90% CI]
Indacaterol	AUC _{0-tlast} (h•pg/mL)	1.25 [1.13,1.37]
	AUC ₀₋₂₄ (h•pg/mL)	1.25 [1.18,1.32]
	C _{max} (pg/mL)	1.49 [1.37,1.62]
NVA237	AUC _{0-tlast} (h•pg/mL)	0.92 [0.78,1.10]
	AUC ₀₋₂₄ (h•pg/mL)	0.98 [0.85,1.12]
	C _{max} (pg/mL)	0.93 [0.78,1.11]

(Source: Table 3, Study QVA149A2101 report)

Table 10. Relative bioavailability of indacaterol and NVA237 after administration as a free combination relative to administration of each compound alone

Compound	Parameter (units)	Ratio Free combo/Alone [90% CI]
Indacaterol	AUC _{0-tlast} (h•pg/mL)	1.14 [1.03,1.26]
	AUC ₀₋₂₄ (h•pg/mL)	1.12 [1.06,1.19]
	C _{max} (pg/mL)	1.18 [1.09,1.29]
NVA237	AUC _{0-tlast} (h•pg/mL)	1.01 [0.85,1.20]
	AUC ₀₋₂₄ (h•pg/mL)	1.00 [0.87,1.15]
	C _{max} (pg/mL)	1.15 [0.97,1.37]

(Source: Table 4, Study QVA149A2101 report)

Table 11. Relative bioavailability of indacaterol and NVA237 after administration of QVA149 relative to administration as a free combination

Compound	Parameter (units)	Ratio QVA149/Free combo [90% CI]
Indacaterol	AUC _{0-tlast} (h•pg/mL)	1.09 [0.99,1.21]
	AUC ₀₋₂₄ (h•pg/mL)	1.11 [1.05,1.17]
	C _{max} (pg/mL)	1.26 [1.16,1.37]
NVA237	AUC _{0-tlast} (h•pg/mL)	0.92 [0.77,1.09]
	AUC ₀₋₂₄ (h•pg/mL)	0.98 [0.85,1.12]
	C _{max} (pg/mL)	0.81 [0.68,0.96]

(Source: Table 5, Study QVA149A2101 report)

Conclusions

- AUC_{0-tlast} of NVA237 was similar after administration of QVA149, the free combination form, and NVA237 alone. C_{max} to NVA237 was similar after administration of QVA149 and NVA237 alone, but was 19% lower for QVA149 compared to the free combination form.
- AUC_{0-tlast} and C_{max} to indacaterol were 25% and 49%, respectively, higher for QVA149 compared to indacaterol alone.
- AUC_{0-tlast} and C_{max} to indacaterol was 14% and 18%, respectively, higher for the free combination form compared to indacaterol alone.
- AUC_{0-tlast} and C_{max} to indacaterol were 9% and 26%, respectively, higher for QVA149 compared to the free combination form.
- The increased exposure to indacaterol following the administration of QVA149 compared to both indacaterol alone and the free combination form is thought to be (b) (4) in the QVA149 formulation.
- All treatments were safe and well tolerated.

Reviewer's comments: *The observed increase in systemic exposure to indacaterol following the administration of QVA149 was believed to be a consequence of quality change in formulation. A relative bioavailability study, Study QVA149A2107, was conducted using the proposed to-be-marketed strength and indicated that the steady-state systemic exposure to QAB149 and NVA237 are similar when administered alone or in fixed-dose combination (as QVA149 27.5/12.5 mcg) in HVs. Refer to Study QVA149A2107 individual study review.*

PK study in HV

Study CQVA149A2103

Title: An open-label, randomized, three-way crossover study to compare the systemic exposure of multiple inhaled doses of indacaterol (QAB149) and glycopyrronium bromide (NVA237) when administered alone or in fixed combination (QVA149) in healthy subjects

Objectives

Primary: To compare the steady-state systemic exposure of QAB149 after administration of QVA149 (110 mcg QAB149 and 50 mcg NVA237) relative to the administration of QAB149 (150 mcg) alone in HVs

Secondary:

- To compare the steady-state systemic exposure of NVA237 after administration of QVA149 (110 mcg QAB149 and 50 mcg NVA237) relative to NVA237 (50 mcg) alone in HVs
- To assess the safety and tolerability

Study Design and Treatment Schedule:

This was an open label, randomized, three-way cross-over study. Each subject participated in a screening period, three baseline periods, three treatment periods of 14 days dosing with a washout of at least seven days between two consecutive treatment periods and a study completion evaluation.

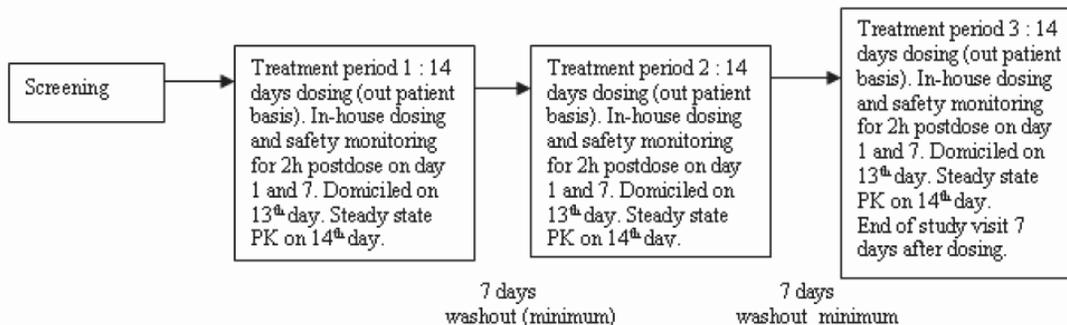


Figure 4. Study design

(Source: Figure 9-1, Study QVA149A2103 report)

Study treatment consisted of the following three arms:

- **Treatment 1:** 1 x 150 mcg QAB149 inhalation QD for 14 days
- **Treatment 2:** 1 x 50 mcg NVA237 inhalation QD for 14 days
- **Treatment 3:** 1 x QVA149 (110 mcg QAB149 and 50 mcg NVA237) inhalation QD for 14 days

All the subjects were to receive all three treatments and were randomized to one of six sequences as Table 12.

Table 12. Study treatment sequence

	Period 1	Period 2	Period 3
Sequence A	QAB149	NVA237	QVA149
Sequence B	NVA237	QVA149	QAB149
Sequence C	QVA149	QAB149	NVA237
Sequence D	QAB149	QVA149	NVA237
Sequence E	QVA149	NVA237	QAB149
Sequence F	NVA237	QAB149	QVA149

(Source: Table 9-1, Study QVA149A2103 report)

Table 13. Test Products

Study Drugs	Batch #
QAB149 0.150 mg hard gelatin capsule inhalation	X358JD
NVA237 0.05 mg hard non-gelatin capsule inhalation	X088 0408
QVA149 0.11+ 0.05 mg hard non-gelatin capsule inhalation	X101 0408
Placebo 0 mg hard non-gelatin capsule inhalation	NA

PK Sampling Schedule

Blood samples for the analysis of QAB149 and NVA237 in plasma were collected at the following time points:

- Predose samples on Day 1 (in Period 1 only), Day 12 and Day 13

- Day 14: pre-dose (0) , 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose

Results

A total of 43 subjects were enrolled in the study and 41 subjects were included in the PK analysis. The key PK parameters of QAB149 and NVA237 and statistical analysis are shown in the Tables 14-16.

Table 14. PK parameters of QAB149 when administered alone or in fixed dose combination (QVA149) in healthy volunteers on Day 14

PK parameter	Arithmetic mean (\pm SD)	
	QAB149 (n=39)	QVA149 (n=38)
AUC _{0-24h} (h.pg/mL)	2007 (547.81)	2164 (528.34)
C _{max,ss} (pg/mL)	321.5 (106.16)	393.9 (100.39)
C _{min,ss} (pg/mL)	51.38 (17.93)	59.77 (17.75)
C _{av,ss} (pg/mL)	83.63 (22.83)	90.16 (22.02)
T _{max,ss} (h) ¹⁾	0.25 (0.25-0.50)	0.25 (0.25-0.25)
Fluc (%)	321.1 (68.61)	374.2 (75.68)

¹⁾ Median (range: [min; max]) for T_{max,ss}
(Source: Table 2-1, Study QVA149A2103 report)

Table 15. PK parameters of NVA237 when administered alone or in fixed dose combination (QVA149) in healthy volunteers on Day 14

PK parameter	Arithmetic mean (\pm SD)	
	NVA237 (n=39)	QVA149 (n=38)
AUC _{0-24h} (h.pg/mL)	396.1 (144.47)	525.4 (128.54)
C _{max,ss} (pg/mL)	117.1 (57.29)	166.6 (75.59)
C _{min,ss} (pg/mL)	10.14 (4.56)	13.60 (3.79)
C _{av,ss} (pg/mL)	16.50 (6.02)	21.89 (5.35)
T _{max,ss} (h) ¹⁾	0.08 (0.08-0.25)	0.08 (0.08-0.08)
Fluc (%)	649.7 (265.26)	700.6 (269.61)

¹⁾ Median (range: [min; max]) for T_{max,ss}
(Source: Table 2-2, Study QVA149A2103 report)

Table 16. Summary of statistical analysis of plasma PK parameters on Day 14

Compound	Parameter	Ratio of geometric means QVA149 / Alone [90% CI]
Indacaterol (QAB149)	AUC _{0-24h}	1.08 [1.04,1.13]
	C _{max,ss}	1.24 [1.16,1.32]
NVA237	AUC _{0-24h}	1.34 [1.26,1.42]
	C _{max,ss}	1.42 [1.26,1.61]

(Source: Table 2-3, Study QVA149A2103 report)

Conclusions

- AUC_{0-24h,ss} to QAB149 was similar for QVA149 110/50 mcg compared to QAB149 150 mcg alone. Apparent C_{max,ss} of QAB149 was, on average, 24% higher for QVA149 than for QAB149.

- AUC_{0-24h,ss} and C_{max,ss} of NVA237 was higher (by 34% and 42%, respectively) after administration of QVA149 110/50 mcg compared to NVA237 50 mcg alone.
- Median T_{max,ss} of both QAB149 (15 min) and NVA237 (5 min) was observed at the same time after inhalation of either the fixed-dose combination or the respective mono formulation.
- All treatments were safe and well tolerated.

Intrinsic Factor

Study QVA149A2104

Title: A single-center, open-label study to investigate the systemic exposure of indacaterol (QAB149) and glycopyrronium (NVA237) following multiple daily inhalation of QVA149 (fixed dose combination of 110 mcg QAB149 and 50 mcg NVA237) in healthy Chinese subjects.

Objectives

Primary: To assess the PK of QVA149 (110 mcg QAB149 and 50 mcg NVA237) following multiple, once-daily inhaled administrations in healthy Chinese subjects.

Secondary: Safety and efficacy

Study Design and Treatment Schedule: This was an open-label, multiple dosing study in healthy Chinese subjects. ~12 subjects were recruited to have at least eight subjects complete the study, following the Chinese regulatory requirements. Following an overnight fast of at least 10 hours, eligible subjects entered treatment period for dosing. QVA149 110/50 mcg was administered using Concept1 in the morning on Day 1 after pre-dose PK blood sampling was taken. Post-dose PK samples up to 24 hours post dose were collected (Figure 5).

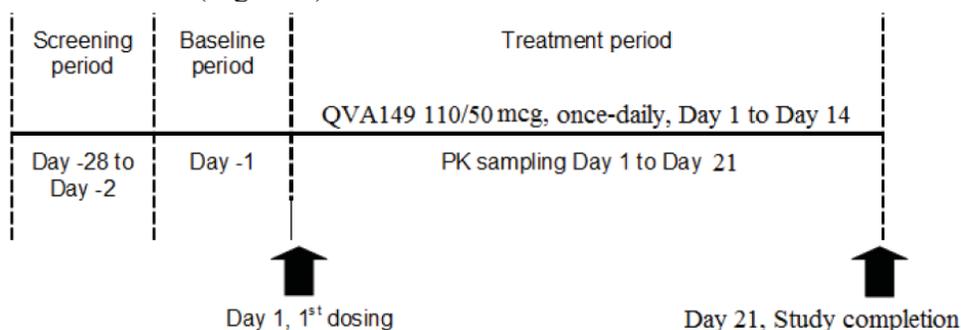


Figure 5. Study design

(Source: Figure 9-1, Study QVA149A2104 report)

Table 17. Test Product

Study drug and strength	Formulation control number	Batch number
QVA149 (110/50 mcg) inhalation powder hard capsules	6002585.008	X105EI

(Source: Table 9-1, Study QVA149A2104 report)

PK Sampling Schedule

Day 1: pre-dose (0), 5, 15, 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post dose (day 2 pre-dose)

Days 5, 7, 10 and 12: pre-dose (trough)

Day 14: pre-dose (0), 5, 15, 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96*, 120* and 168* hours post-dose (*For QAB149 collection only)

Results

The PK profiles and PK parameters of QAB149 and NVA237 are shown in Figures 6 and 7 and Table 18 and 19.

QAB149: Following QVA149 (110/50 mcg) inhalation, T_{max} of QAB149 was 15 min post dose after both single and multiple QD dose. QAB149 plasma concentrations of showed a steep decrease for up to 4-8 hours and a slower decrease thereafter. The observed accumulation ratio (R_{acc}) of the AUC_{0-24h} (Day14/Day1) was 3.02 ± 0.543 . The estimated mean accumulation ratio of C_{max} from Day 1 to Day 14 was ~1.56. The terminal elimination half-life (T_{1/2}) could not be accurately determined because the individual plasma concentration-time profiles did not show a continuous decline in plasma concentrations during the terminal phase. QAB149 PK steady-state conditions were reached after 12 days of daily dosing with QVA149.

NVA237: Following QVA149 (110/50 mcg) inhalation, T_{max} of NVA237 was 5 min post dose after both single and multiple QD dose. NVA237 plasma concentrations of showed a steep decrease for up to 4-8 hours and a slower decrease thereafter. The observed accumulation ratio (R_{acc}) of the AUC_{0-24h} (Day14/Day1) was 2.94 ± 0.686 . The estimated mean accumulation ratio of C_{max} from Day 1 to Day 14 was ~1.33. The terminal elimination half-life (T_{1/2}) could not be accurately determined because the individual plasma concentration-time profiles did not show a continuous decline in plasma concentrations during the terminal phase. NVA237 PK steady-state conditions were reached after 10 days of daily dosing with QVA149.

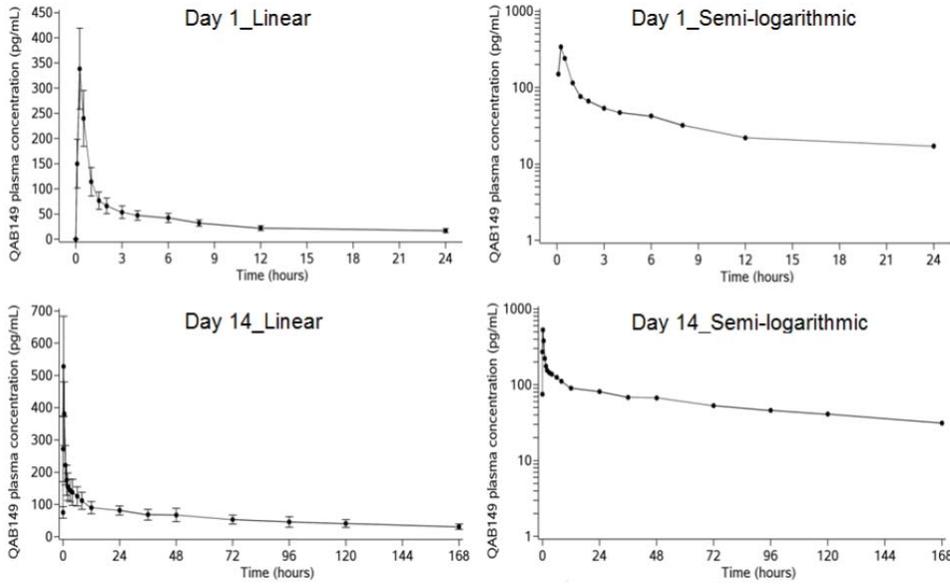


Figure 6. Mean plasma concentration-time profiles of QAB149 on Day 1 and Day 14
 (Source: Figure 11-1, Study QVA149A2104 report)

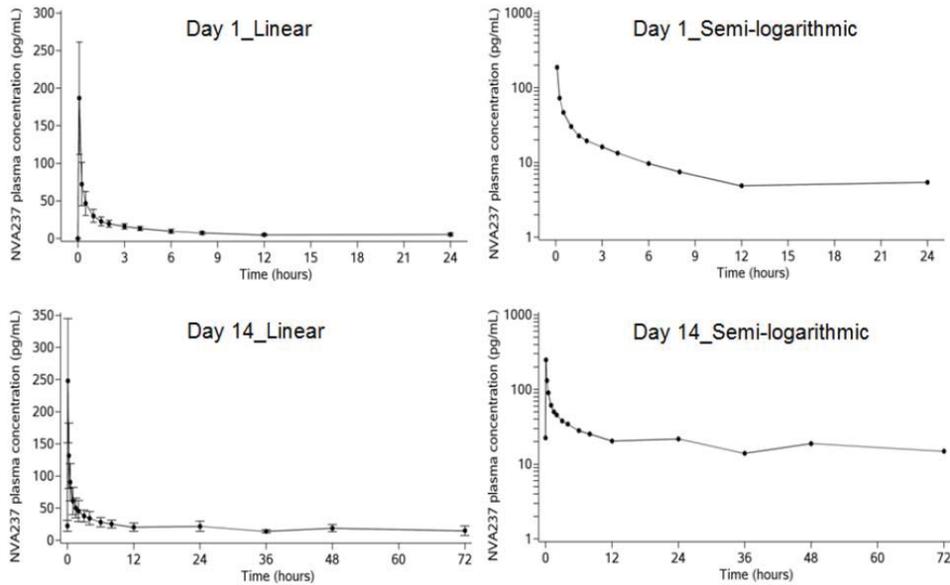


Figure 7. Mean plasma concentration-time profiles of NVA237 on Day 1 and Day 14
 (Source: Figure 11-2, Study QVA149A2104 report)

Table 18. Summary of PK parameters of QAB149 and NVA237 on Day 1

PK parameter (unit)	QAB149	NVA237
	Mean ± SD (% CV) [n]	Mean ± SD (% CV) [n]
AUC0-24h (hr*pg/mL)	907 ± 185 (20.4) [12]	246 ± 68.9 (28.0) [12]
Cmax (pg/mL)	339 ± 80.2 (23.7) [12]	187 ± 75.0 (40.2) [12]
Tmax (hr)*	0.25 (0.25-0.25) [12]	0.08 (0.08-0.08) [12]

Source: [Table 14.2-2.1](#) and [Table 14.2-2.2](#)

*Median (Min - Max) [n]

(Source: Table 11-2, Study QVA149A2104 report)

Table 19. Summary of PK parameters of QAB149 and NVA237 on Day 14

PK parameter (unit)	QAB149	NVA237
	Mean ± SD (% CV) [n]	Mean ± SD (% CV) [n]
Cmin,ss (pg/mL)	73.5 ± 15.7 (21.3) [11]	19.3 ± 6.44 (33.4) [11]
Cmax,ss (pg/mL)	528 ± 156 (29.5) [11]	248 ± 96.8 (39.0) [11]
AUC0-24h,ss (hr*pg/mL)	2750 ± 616 (22.4) [11]	698 ± 211 (30.3) [11]
Tmax (hour)*	0.25 (0.25-0.25) [11]	0.08 (0.08-0.08) [11]
Cav,ss (pg/mL)	114 ± 25.7 (22.4) [11]	29.1 ± 8.80 (30.3) [11]
T1/2,acc (hr)	41.3 ± 9.17 (22.2) [11]	40.0 ± 11.6 (29.0) [11]
Racc	3.02 ± 0.543 (18.0) [11]	2.94 ± 0.686 (23.3) [11]
Fluc (%)	393 ± 51.9 (13.2) [11]	778 ± 139 (17.9) [11]

Source: [Table 14.2-2.3](#) and [Table 14.2-2.4](#)

*Median (Min - Max) [n]

(Source: Table 11-3, Study QVA149A2104 report)

Conclusions

- QAB149 and NVA237 were absorbed shortly after inhalation of QVA149 110/50 mcg. Median Tmax on both Days 1 and 14 were reached 15 minutes and 5 minutes after inhalation, respectively.
- Following multiple QD inhalation of QVA149 for 14 days, the mean accumulation ratios (Racc) of AUC0-24h (Day 14/ Day 1) for QAB149 and NVA237 were 3.02 and 2.94 respectively. The PK steady-states of QAB149 and NVA237 were reached after 12 and 10 days of QD dosing respectively.

PD and PK/PD study in HV

Study QVA149A2105

Title: A double-blind, randomized, placebo and active drug controlled, incomplete cross-over study to investigate the secondary pharmacodynamic effects, the pharmacokinetics, safety and tolerability of QVA149 in healthy volunteers

Objectives:

Primary: To estimate the effect of cumulative doses of QVA149 in terms of time-matched largest (peak) heart rate change from baseline and average heart rate change from baseline over 24h as compared to placebo.

Secondary:

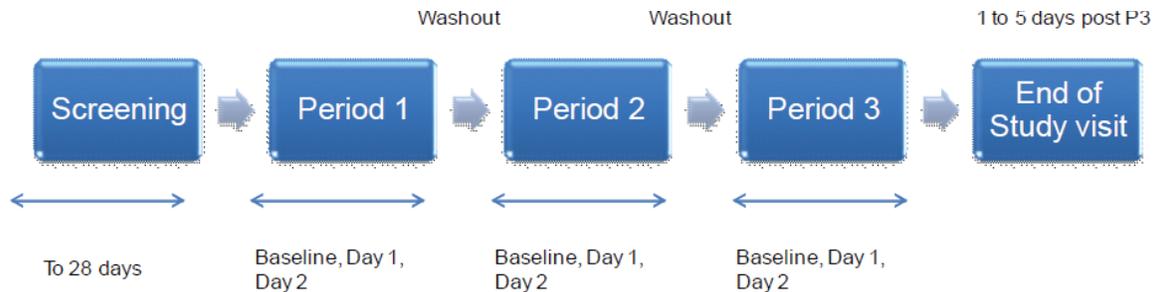
- To investigate the effect of QVA149 on heart rate
- To assess the effects of the treatments on further secondary PD-read-outs
- To estimate the systemic exposure of QAB149 and NVA237 in QVA149 and monotherapies and of salmeterol
- To assess the safety and tolerability

Study Design and Treatment Schedule:

This was a double-blind, randomized, placebo and active drug controlled incomplete 3-period cross-over study in healthy volunteers (Figure 8). Each single dose was administered in four steps separated by one hour (This means that the first dose step was given at 0 h and the last dose step was given at + 3h).

Salmeterol was chosen as the active comparator as it is a registered long-acting bronchodilator that is frequently used by COPD patients. Heart rate increases have been described in the Serevent prescribing information. The component drugs of QVA149 (QAB149 and NVA237) were also administered as comparators in order to determine the contribution of these monotherapy components on the PD effect. Placebo was used as a comparator in order to account for potential placebo effects.

In order to maintain the blind subjects received Diskus placebo when taking treatments with the Concept1 device and received Concept1 placebo when taking salmeterol and took placebo from both devices when receiving placebo.



Washout between periods is for 14-21 days

Figure 8. Study design
(Source: Figure 9-1, Study QVA149A2105)

Table 20. Treatment sequences

Sequence	Period 1	Period 2	Period 3
1	QVA149 Diskus Placebo	NVA237 Diskus Placebo	QAB149 Diskus Placebo
2	Concept1 Placebo Diskus Placebo	QVA149 Diskus Placebo	NVA237 Diskus Placebo
3	NVA237 Diskus Placebo	Salmeterol Concept1 Placebo	QVA149 Diskus Placebo
4	QVA149 Diskus Placebo	QAB149 Diskus Placebo	Concept1 Placebo Diskus Placebo
5	Salmeterol Concept1 Placebo	QVA149 Diskus Placebo	QAB149 Diskus Placebo
6	Concept1 Placebo Diskus Placebo	Salmeterol Concept1 Placebo	QVA149 Diskus Placebo
7	NVA237 Diskus Placebo	QAB149 Diskus Placebo	Concept1 Placebo Diskus Placebo
8	QAB149 Diskus Placebo	NVA237 Diskus Placebo	Salmeterol Concept1 Placebo
9	Salmeterol Concept1 Placebo	Concept1 Placebo Diskus Placebo	NVA237 Diskus Placebo
10	QAB149 Diskus Placebo	Concept1 Placebo Diskus Placebo	Salmeterol Concept1 Placebo

Both treatments were given on day 1 in double dummy design

(Source: Table 9-1, Study QVA149A2105)

Table 21. Test Product

Treatment	Strength	Batch #
QVA149 (fixed dose combination of 440 mcg QAB149/200 mcg NVA237)	110 mcg QAB149/50 mcg NVA237 x 4 steps	X259LF
QAB149 600 mcg	150 mcg x 4 steps	X138DG
NVA237 200 mcg	50 mcg x 4 steps	X325LG
Matching placebo for use in Concept1 inhaler	x 4 steps	X137EF
Salmeterol 200 mcg	50 mcg x 4 steps	1315A, 1404
Matching placebo to salmeterol	x 4 steps	X2770807

PD Assessment

Heart rate and QTcF assessment: Holter ECG recordings over 27 hours were used for heart rate and QTcF assessments. These were collected starting 1 hour prior to the first dose until 27 hours after the first dose step on day 1 of each period.

Serum potassium and glucose measurement:

Blood samples were taken at baseline and at 2hr 10min, 4hr 10min, 6hr 10min and at 8hr 10min in treatment period for serum potassium measurement.

Blood samples were taken at baseline and at 4hr 10min, 6hr 10min and at 8hr 10min in treatment period for blood glucose measurement.

PK Sampling Schedule

Blood samples were collected in each treatment period at predose (0), 5 min, 15 min, 50min, 1h 5min, 1h 15min, 1h 50min, 2h 5min, 2h 15min, 2h 50min, 3h 5min, 3h 15min, 3h 50min, 4h 30min, 5h, 5h 30min, 6h, 8h, 12h, 24h, and 27h.

Results

PD results

Primary PD results

The primary PD variables were the largest time-matched heart rate change from baseline and the average heart rate change from baseline for the primary contrast of QVA149 versus placebo.

Increases in heart rate were observed up to 3h 55 m with QVA149 when compared to placebo when decreases were observed although for the majority of these changes the 90% CI included zero. The largest mean increase of 5.69 bpm (90% CI: 2.71, 8.66 bpm) was observed at 1h 10m post dose with the upper 90% CI being below 10 bpm. The largest mean decrease of - 2.51 bpm (90%CI: -5.48, 0.47) (Table 22).

Table 22. Treatment of change from baseline in heart rate by time point for QVA149 versus placebo

Scheduled timepoint	Least square mean difference	90% CI
00h 10m	2.16	-0.84, 5.16
00h 55m	0.52	-2.45, 3.50
01h 10m	5.69 ⁱ	2.71, 8.66
01h 30m	4.00	1.02, 6.97
01h 55m	1.16	-1.81, 4.14
02h 10m	1.67	-1.31, 4.64
02h 30m	0.77	-2.20, 3.75
02h 55m	0.45	-2.55, 3.45
03h 10m	2.48	-0.52, 5.48
03h 30m	0.61	-2.37, 3.58
03h 55m	1.79	-1.21, 4.79
04h 10m	-2.51 ^d	-5.48, 0.47
04h 35m	-1.15	-4.13, 1.82
05h 05m	-1.03	-4.01, 1.94
05h 35m	-2.34	-5.32, 0.63
06h 05m	-1.08	-4.06, 1.89
08h 05m	-0.79	-3.77, 2.18
12h 05m	-1.40	-4.37, 1.58
16h 05m	0.30	-2.69, 3.29
24h 00m	1.59	-1.41, 4.58
27h 00m	0.05	-2.94, 3.04

ⁱ = largest mean increase; ^d = largest mean decrease
(Source: Table 11-2, Study QVA149A2105 report)

Secondary PD results

Secondary contrasts for HR: The largest change in HR decreased when QVA149 was compared to both QAB149 and salmeterol, but increased when QVA149 was compared to NVA237 (Table 23).

Table 23. Change from baseline in HR (bpm) averaged over time for secondary treatment comparisons

Treatment comparison	Least square mean difference	90% CI
QVA149 vs QAB149	-3.33	-4.89, -1.76
QVA149 vs NVA237	1.78	0.20, 3.37
QVA149 vs salmeterol	-6.83	-8.47, -5.20

(Source: Table 11-4, Study QVA149A2105 report)

QTcF interval: There were no consistent QTcF differences when QVA149 was compared to QAB149, NVA237 and a slight trend towards lower QTcF values when compared to salmeterol (Table 24).

Table 24. Time-matched largest mean change from baseline in QTcF (ms) for all treatment comparisons

Treatment comparison	Timepoint	Time-matched mean difference	90% CI
QVA149 vs Placebo (Increase)	01h 30m	4.62	(0.40, 8.85)
QVA149 vs Placebo (Decrease)	16h 05m	-2.71	(-6.97, 1.54)
QVA149 vs QAB149 (Increase)	03h 55m	4.88	(0.59, 9.17)
QVA149 vs QAB149 (Decrease)	05h 05m	-2.66	(-6.91, 1.59)
QVA149 vs NVA237 (Increase)	03h 55m	6.42	(2.05, 10.79)
QVA149 vs NVA237 (Decrease)	24h 00m	-1.37	(-5.67, 2.93)
QVA149 vs salmeterol (Decrease)	08h 05m	-5.86	(-10.23, -1.50)
QVA149 vs salmeterol (Increase)	12h 05m	2.12	(-2.28, 6.51)

(Source: Table 11-5, Study QVA149A2105 report)

Serum Potassium: QVA149 did not show a clinically relevant effect on serum potassium. The largest difference observed when compared to placebo was 0.14 mmol/l.

Blood Glucose: A small effect of QVA149 was observed on blood glucose when compared to placebo, the maximum difference being 0.67 mmol/l. There were no differences between QVA149 and QAB149. The largest difference to NVA237 was 1.13 mmol/l.

PK results

The component analytes from the FDC (QAB149 and NVA237) and the corresponding monotherapy analytes were absorbed rapidly following each inhalation of QVA149, QAB149 and NVA237. The median Tmax was 15 minutes post fourth dose for QAB149 and 5 minutes post fourth dose for NVA237 in combination (QVA149) as well as in respective monotherapy. Systemic exposure (AUClast, AUC0-24h and Cmax) to

NVA237 given in combination (QVA149) was 7 to 11 % greater than for NVA237 administered alone. For QAB149 given in combination (QVA149), systemic exposure (AUC_{last}, AUC_{0-24h} and C_{max}) was 11 to 14 % less than for QAB149 given alone (Table 25 and Figure 9).

It should be noted that parameters related to the elimination rate constant (T_{1/2}, CL/F, V_z/F, AUC_{inf}) could not be determined for QAB149 or NVA237 because samples were only collected for 24 hours post the final dose step and therefore the time interval to capture the terminal elimination phase was too short.

Table 25. Summary statistics of key PK parameters of QAB149 and NVA237 by treatment

PK parameter (unit)	Statistic	QVA149			
		QAB149 N=26	NVA237 N=25	QAB149 N=29	NVA237 N=29
AUC _{last} (h*pg/mL)	Mean (SD)	2680 (598)	1090 (214)	3100 (845)	1020 (209)
	CV%	22.3	19.5	27.3	20.5
C _{max} (pg/mL)	Mean (SD)	458 (102)	355 (85.9)	515 (118)	321 (90.2)
	CV%	22.3	24.2	22.9	28.1
T _{max} (h)	Median	3.25	3.08	3.25	3.08
	Range	2.25, 3.27	1.08, 3.18	2.25, 3.30	1.08, 3.12
	Mean (SD)	2550 (571)	1050 (207)	2950 (804)	970 (200)
AUC _{0-24h} (h*pg/mL)	CV%	22.4	19.8	27.3	20.6

Treatment: QVA149 (440µg QAB149 + 200µg NVA237). 600µg QAB149, 200µg NVA237
(Source: Table 11-6, Study QVA149A2105 report)

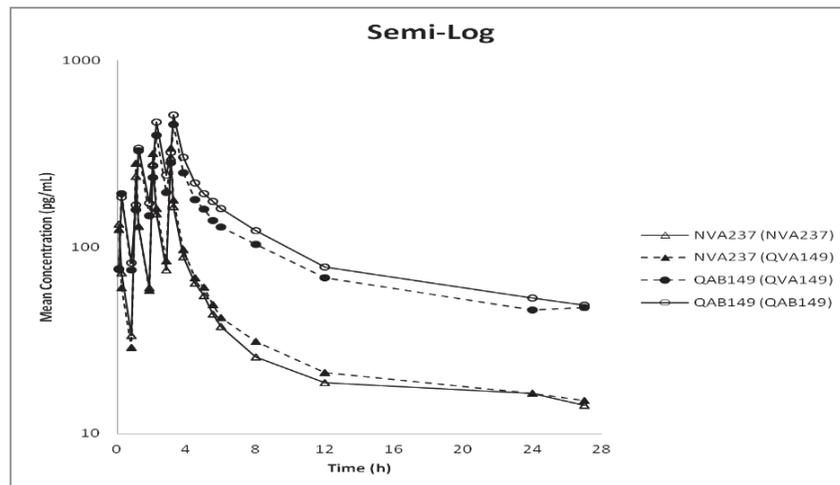


Figure 9. Arithmetic mean plasma concentration-time profile (0-27 h) for QVA149, QAB149 and NVA237

(Source: Figure 11-2, Study QVA149A2105 report)

PK/PD relationship

The relationship between concentration and cardiac parameters, heart rate and QTcF was investigated. There was no relationship between the time course of drug concentrations of QAB149, NVA237 and salmeterol and the effects on heart rate and QTcF vs. baseline in

any treatment. There was no apparent PK/PD relationship between AUClast and Cmax and changes in heart rate and QTcF for any treatment.

Conclusions

- QVA149 at dose of 440 mcg QAB149/200 mcg NVA237 had no relevant effect on heart rate when compared to placebo.
- There was no tachycardic potential of QVA149 when compared to QAB149 alone and there was no relevant tachycardic effect when QVA149 was compared with NVA237 alone.
- When QVA149 was compared to salmeterol, the heart rate effect was lower.
- QVA149 had no relevant effect vs. placebo with regards to QTcF.
- A small effect of QVA149 was observed on blood glucose when compared to placebo. There were no differences between QVA149 and QAB149.
- The difference in systemic exposure for NVA237 and QAB149 given in combination product QVA149 and monotherapies alone is not of clinical relevance.
- There was no apparent relationship between the observed exposures to QAB149 and NVA237 in QVA149 and heart rate and QTcF.
- QVA149 was safe and well tolerated by the healthy subjects at 440 mcg QAB149/200 mcg NVA237.

For further details refer to QT/IRT review for NDA207930.

PK study in HV

Study CQVA149A2106

Title: An open-label, randomized, four-period crossover study to compare the systemic exposure of multiple inhaled doses of indacaterol (QAB149) and NVA237 when administered alone, in free, or in fixed combination (QVA149) in healthy subjects

Objectives:

Primary

- Compare the steady-state systemic exposure of QAB149 and NVA237 after administration of QVA149 (QAB149 110mcg /NVA237 50 mcg) and QAB149 150 mcg or NVA237 50 mcg alone in HVs

Secondary

- Compare the steady-state systemic exposure of QAB149 and NVA237 after administration in a free combination of 150 mcg QAB149 and 50 mcg NVA237 relative to the administration of indacaterol 150 mcg and NVA237 50 mcg alone in HVs
- Compare the steady-state systemic exposure of QAB149 and NVA237 after administration in a fixed dose combination as QVA149 (110 mcg QAB149 and 50 mcg NVA237) relative to the administration of a free combination of 150 mcg QAB149 and 50 mcg NVA237 in HVs
- Safety and tolerability

Study Design and Treatment Schedule: This study employed an open-label, randomized, four-period, cross-over design. Each subject participated in a 21-day screening period, four baseline periods, four treatment periods comprising 14 days dosing, with a washout period of at least seven days between two consecutive treatment periods, and a study completion evaluation (5 - 9 days after the last dosing). Subjects were randomized to receive all four treatments (Figure 10 and Table 26).

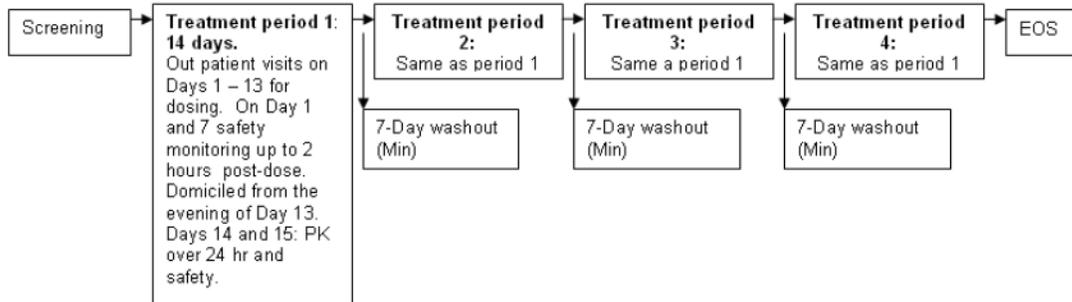


Figure 10. Study design.

(Source: Figure 9-1, Study QVA149A2106 report)

Study treatment consisted of the following four arms:

- Treatment 1: 150 mcg QAB149 inhalation QD for 14 days
- Treatment 2: 50 mcg NVA237 inhalation QD for 14 days
- Treatment 3: Free combination of 150 mcg QAB149 and 50 mcg NVA237 inhalation QD for 14 days (Note: NVA237 was inhaled first and then QAB149).
- Treatment 4: QVA149 110/50 (fixed dose combination of 110 mcg QAB149 and 50 mcg NVA237), one inhalation capsule once daily for 14 days

Table 26. Study treatment sequences

	Period 1*	Period 2*	Period 3*	Period 4*
Sequence 1	Treatment 1	Treatment 4	Treatment 2	Treatment 3
Sequence 2	Treatment 2	Treatment 1	Treatment 3	Treatment 4
Sequence 3	Treatment 3	Treatment 2	Treatment 4	Treatment 1
Sequence 4	Treatment 4	Treatment 3	Treatment 1	Treatment 2

* Washout period of at least 7 days between each period.

(Source: Table 9-1, Study QVA149A2106 report)

Table 27. Test Products

Treatment	Product	Device	Strength	Batch#
1	QAB149, 150 mcg	Concept1	150 mcg	X262KE
2	NVA237, 50 mcg	Concept1	50 mcg	X288ME
3	Free combination: QAB149 150 mcg and NVA237 50 mcg	Concept1	QAB149 150 mcg; NVA237 50 mcg	X262KE X288ME
4	Fixed dose combination QVA149 (QAB149 110 mcg/NVA237 50 mcg)	Concept1	QVA149 (110/50 mcg)	X136EF

PK Sampling Schedule

Days 1, 12, 13: predose

Day 14: 0 (predose), 5 min, 15 min, 30 min and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose.

Results

The PK results and statistical analysis were shown in Tables 28-30.

QAB149: The plasma concentrations of QAB149 were similar for QAB149 given alone (QAB149 150 mcg) and the free combination of QAB149 and NVA237 ((QAB149 150 mcg and NVA237 50 mcg), but on average about 20% lower for QVA149 (QAB149110 mcg/ NVA23750 mcg). The observed systemic exposure ratio could be explained by the higher nominal dose of QAB149 in the QAB149 mono formulation as compared to QVA149 and the absorption characteristics of QAB149.

NVA237: The plasma concentrations of NVA237 were similar across all three treatments, i.e. NVA237 given alone (NVA237 (50 mcg)), the free combination of QAB149 and NVA237 (QAB149 150 mcg and NVA237 50 mcg), and QVA149 (QAB149110 mcg/ NVA237 50 mcg).

Table 28. Summary of PK parameters of QAB149 per treatment on Day 14: mean (SD)

Parameter	QVA149 (n=23)	Free combination (n=22)	QAB149 alone (n=24)
AUC _{0-24h} (hr•pg/mL)	2024 (591.87)	2568 (648.74)	2616 (656.78)
C _{max,ss} (pg/mL)	371.4 (118.90)	477.8 (156.40)	454.6 (131.69)
C _{min,ss} (pg/mL)	54.65 (14.97)	67.02 (15.68)	65.55 (16.45)
C _{av,ss} (pg/mL)	85.67 (23.50)	107.0 (27.06)	108.9 (27.35)
T _{max,ss} (hr) ¹⁾	0.25 (0.08-0.27)	0.25 (0.23-0.53)	0.25 (0.25-0.25)
Fluc (%)	367.6 (66.54)	381.5 (94.54)	356.2 (66.79)

¹⁾ Median (range: [min; max]) for T_{max,ss}

(Source: Table 1, Study QVA149A2106 report)

Table 29. Summary of PK parameters of NVA237 per treatment on Day 14: mean (SD)

Parameter	QVA149 (n=23)	Free combination (n=22)	NVA237 alone (n=24)
AUC _{0-24h} (hr•pg/mL)	566.8 (246.13)	585.2 (217.56)	557.9 (227.51)
C _{max,ss} (pg/mL)	212.3 (133.96)	237.8 (144.19)	216.2 (148.15)
C _{min,ss} (pg/mL)	14.21 (6.39)	14.24 (4.52)	14.90 (5.24)
C _{av,ss} (pg/mL)	23.82 (10.12)	24.37 (9.07)	23.39 (9.14)
T _{max,ss} (hr) ¹⁾	0.08 (0.08-0.25)	0.08 (0.07-0.17)	0.08 (0.08-0.18)
Fluc (%)	788.9 (297.76)	876.9 (360.61)	806.1 (317.18)

¹⁾ Median (range: [min; max]) for T_{max,ss}

(Source: Table 2, Study QVA149A2106 report)

Table 30. Summary of statistical analysis of plasma PK parameters on Day 14 for the three treatment comparisons

Parameter (Unit)	Compound	QVA149/Alone	Free/Alone	QVA149/Free
		Ratio [90% CI]	Ratio [90% CI]	Ratio [90% CI]
AUC _{0-24h} [hr•pg/mL]	QAB149	0.77 [0.72 , 0.82]	0.98 [0.92 , 1.05]	0.78 [0.73 , 0.83]
	NVA237	1.01 [0.94 , 1.09]	1.05 [0.98 , 1.14]	0.96 [0.89 , 1.04]
C _{max,ss} [pg/mL]	QAB149	0.81 [0.74 , 0.90]	1.04 [0.94 , 1.14]	0.78 [0.71 , 0.86]
	NVA237	1.00 [0.85 , 1.17]	1.10 [0.93 , 1.29]	0.91 [0.78 , 1.07]

Alone = QAB149 or NVA237 alone; Free = free combination of NVA237 and QAB149
(Source: Table 3, Study QVA149A2106 report)

Conclusions

Given the same dose, the steady-state systemic exposure to QAB149 and NVA237 are similar following the administration of free combination, mono-treatments, and fixed-dose combination product, suggesting there was no PK drug-drug interaction between QAB149 and NVA237 when both drugs were administered together.

PK study in HV

Study CQVA149A2107

Title: An open-label, randomized, four-period cross-over study to compare the systemic exposure of multiple inhaled doses of indacaterol (QAB149) and glycopyrronium (NVA237) when administered alone or in fixed-dose combination (as QVA149 27.5/12.5 mcg) in healthy volunteers

Objectives

Primary: To compare the steady-state systemic exposures to indacaterol and glycopyrronium after BID administration in a fixed-dose combination as QVA149 27.5/12.5 (27.5 mcg QAB149 and 12.5 mcg NVA237 dry powder inhaler formulation) with those following BID administration of QAB149 27.5 mcg alone and NVA237 12.5 mcg alone.

Secondary

- To establish the relative bioavailability of indacaterol after BID administration in a FDC as QVA149 27.5/12.5 mcg compared to the QD administration of QAB149 75 mcg.
- To assess the safety and tolerability

Study Design and Treatment Schedule: This was an open label, randomized, non-confirmatory, four period crossover study. There were four treatment sequences for the study. Each subject did participate in a screening period (Day -21 to Day -2), four baseline periods, four treatment periods comprising 14 days dosing, with a washout period of at least seven days between two consecutive treatment periods, and a study

completion evaluation (approximately 7 days after the last dosing) (Table 31 and Figure 11).

Table 31. Definition of treatment sequences

Sequence	N	Period 1	Period 2	Period 3	Period 4
1	9	A	D	B	C
2	9	B	A	C	D
3	9	C	B	D	A
4	9	D	C	A	B

(Source: Table 9-1, Study QVA149A2107 report)

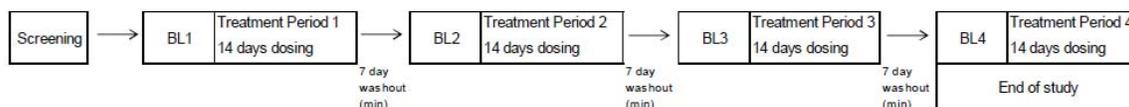


Figure 11. Study design

(Source: Figure 9-1, Study QVA149A2107 report)

For QVA149 27.5/12.5 mcg, QAB149 27.5 mcg, and NVA237 12.5 mcg the content of two capsules each (x 2; i.e. Subjects were required to inhale the contents of 2 capsules using the Concept1 device within 2 minutes at each dosing occasion) was inhaled to allow for the quantification of the analytes in plasma over the concentration-time profile; for consistency the content of two capsules of QAB149 75 mcg (x 2) was inhaled too.

Table 32. Test product

Treatment	Product	Device	Strength	Batch#
A	QVA149 27.5/12.5 mcg x 2 capsules, BID	Concept1	QVA149 27.5/12.5 mcg	X092D1
B	QAB149 27.5 mcg x 2 capsules, BID	Concept1	QAB149 27.5 mcg	X117 0512
C	NVA237 12.5 mcg x 2 capsules, BID	Concept1	NVA237 12.5 mcg	X099E1
D	QAB149 75 mcg x 2 capsules, o.d.	Concept1	QAB149 75 mcg	X041AK

PK Sampling Schedule

Blood collection schedule for PK plasma samples:

- Pre-dose on Day 1
- Pre-morning and if applicable pre-evening on Day 12 and Day 13
- Day 14: Pre-dose (0), 0.083, 0.25, 0.5 hour (5, 15, 30 minutes), and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24* hours post-dose (* For Treatment D only).

Results

QAB149

Results indicated the mean plasma concentration-time profiles of indacaterol were almost superimposed after inhalation of the FDC (QVA149 27.5/12.5 mcg x2) and the

monotherapy (QAB149 27.5 mcg x2). The mean exposure PK parameters AUC_{tau,ss} (corresponding to AUC_{0-12h,ss}), C_{max,ss}, C_{min,ss} and C_{av,ss} of indacaterol were similar for both treatments. The mean degree of fluctuation at steady state was similar for both BID treatments. The median T_{max,ss} was 15 minutes (0.25 hr) postdose in all treatments (Figure 11 and Table 33).

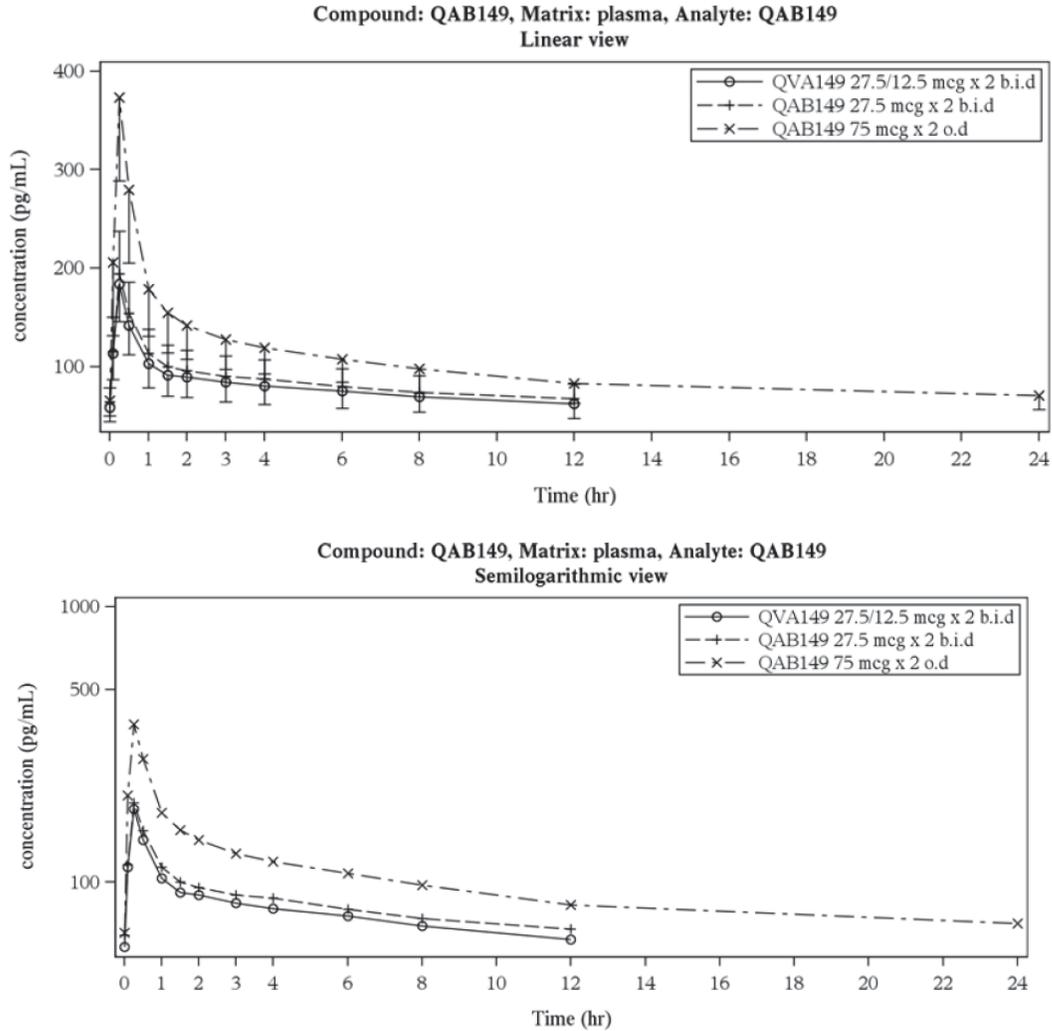


Figure 11. Arithmetic mean (SD) plasma concentration-time profiles of indacaterol per treatment on Day 14

(Source: Figure 11-1, Study QVA149A2107 report)

Table 33. Summary statistics of PK parameters of indacaterol per treatment on Day 14

Treatment	Statistic	AUCtau,ss (h*pg/mL)	Cmax,ss (pg/mL)	Cmin,ss (pg/mL)	Tmax,ss (h)*	Cav,ss (pg/mL)	Fluc (%)
QVA149 27.5/12.5 mcg b.i.d. x2	Mean ±	960 ± 210	184 ± 38.3	56.4 ± 12.9	0.250	80.0 ± 17.5	162 ± 29.2
	SD (%CV) [n]	(21.9)[30]	(20.8)[30]	(22.8)[30]	(0.250;0.250) [30]	(21.9)[30]	(18.0)[30]
QAB149 27.5 mcg b.i.d. x2	Mean ±	1030 ± 214	194 ± 43.4	63.2 ± 13.8	0.250	85.9 ± 17.8	154 ± 34.7
	SD (%CV) [n]	(20.7)[32]	(22.4)[32]	(21.9)[32]	(0.250;0.500) [32]	(20.7)[32]	(22.6)[32]
QAB149 75 mcg o.d. x2	Mean ±	2380 ± 529	374 ± 85.9	64.4 ± 14.3	0.250	99.3 ± 22.1	313 ± 42.3
	SD (%CV) [n]	(22.2)[31]	(23.0)[31]	(22.3)[31]	(0.133;0.267) [31]	(22.2)[31]	(13.5)[31]

(Source: Table 11-3, Study QVA149A2107 report)

NVA237

The mean plasma concentration-time profiles of glycopyrronium (NVA237) were almost superimposable after inhalation of the FDC (QVA149 27.5/12.5 mcg x2) and the monotherapy comparator (NVA237 12.5 mcg x2). The AUCtau,ss (corresponding to AUC0-12h,ss), Cmax,ss, Cmin,ss and Cav,ss of glycopyrronium were similar for both treatments. The mean degree of fluctuation at steady state was similar for both BID treatments. Glycopyrronium was systemically available very shortly after inhalation with median Tmax,ss values of 5 minutes in two treatments (Figure 12 and Table 34).

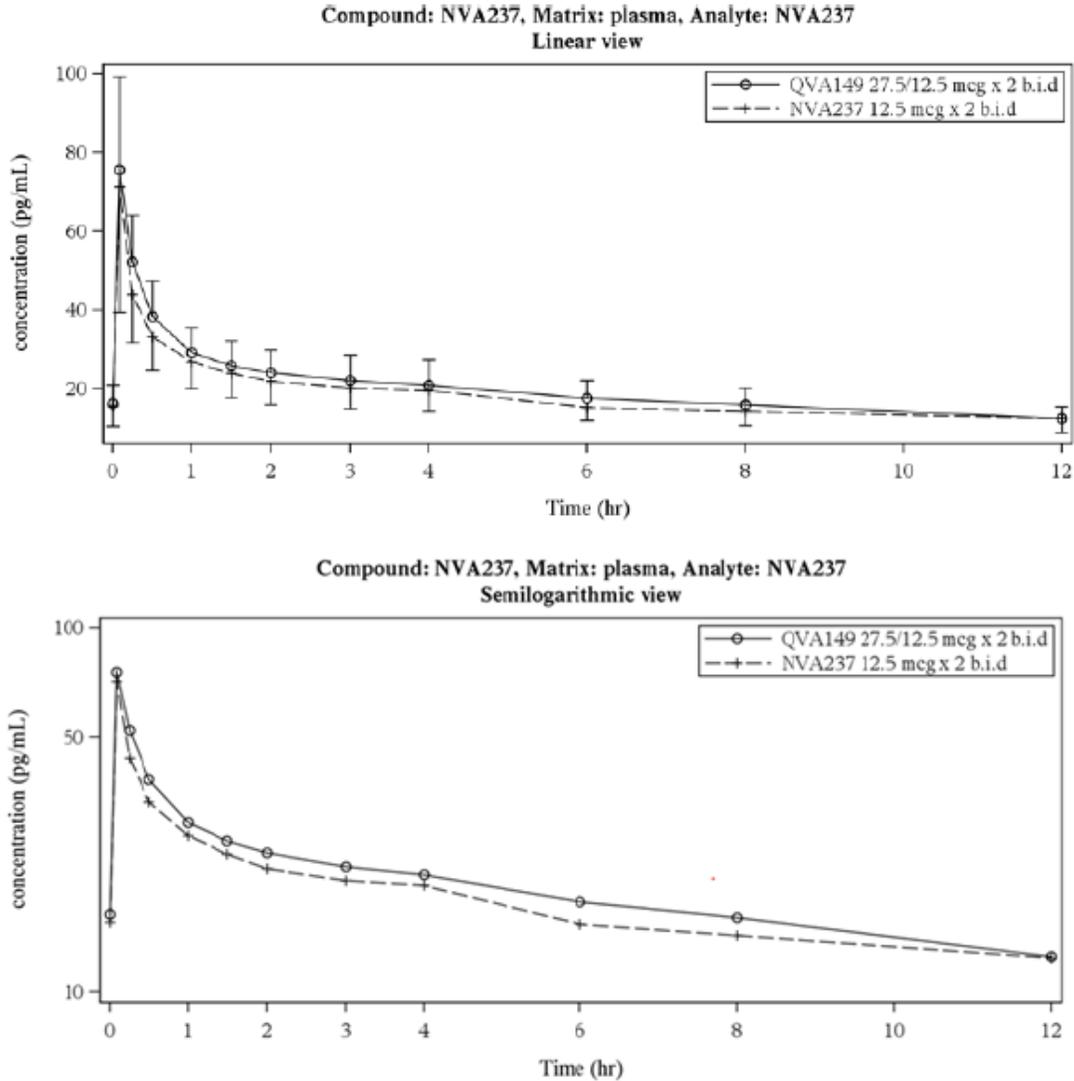


Figure 12. Arithmetic mean (SD) plasma concentration-time profiles of glycopyrronium per treatment on Day 14

(Source: Figure 11-2, Study QVA149A2107 report)

Table 34. Summary statistics of PK parameters of glycopyrronium per treatment on Day 14

Treatment	Statistic	AUC _{tau,ss} (h*pg/mL)	C _{max,ss} (pg/mL)	C _{min,ss} (pg/mL)	T _{max,ss} (h)*	C _{av,ss} (pg/mL)	Fluc (%)
QVA149 27.5/12.5 mcg b.i.d. x2	Mean ± SD (%CV) [n]	243 ±52.4 (21.6)[30]	75.5 ±23.8 (31.5)[30]	12.4 ±2.80 (22.6)[30]	0.0830 (0.0830;0.0830) [30]	20.2 ±4.37 (21.6)[30]	314 ±92.5 (29.5)[30]
NVA237 12.5 mcg b.i.d. x2	Mean ± SD (%CV) [n]	221 ±50.6 (22.9)[32]	71.9 ±31.1 (43.2)[32]	11.8 ±3.47 (29.4)[32]	0.0830 (0.0830;0.250) [32]	18.4 ±4.21 (22.9)[32]	327 ±150 (45.8)[32]

(Source: Table 11-4, Study QVA149A2107 report)

Comparison between monotherapy and FDC

Summary of statistical analysis of indacaterol and glycopyrronium PK parameters are provided in Table 35.

Table 35. Summary of statistical analysis of PK parameters of indacaterol and glycopyrronium using mixed effects model

Analyte	Treatment	PK parameter	Adjusted geometric mean (90% CI)	GMR (90% CI)
QAB149	QVA149 27.5/12.5 mcg (T) vs. QAB149 27.5 mcg (R)	AUC _{0-12,ss} (T) (n=30)	952.53 (891.22, 1018.06)	0.95 (0.91, 0.99)
		AUC _{0-12,ss} (R) (n=32)	1000.52 (937.17, 1068.14)	
		C _{max,ss} (T) (n=30)	183.02 (170.85, 196.06)	0.97 (0.93, 1.02)
		C _{max,ss} (R) (n=32)	187.72 (175.50, 200.79)	
NVA237	QVA149 27.5/12.5 mcg (T) vs. NVA237 12.5 mcg (R)	AUC _{0-12,ss} (T) (n=30)	233.89 (218.53, 250.33)	1.09 (1.05, 1.13)
		AUC _{0-12,ss} (R) (n=32)	214.63 (200.72, 229.50)	
		C _{max,ss} (T) (n=30)	70.19 (62.68, 78.60)	1.07 (0.97, 1.18)
		C _{max,ss} (R) (n=32)	65.55 (58.72, 73.19)	
QAB149	QVA149 27.5/12.5 mcg (T) vs. QAB149 75mcg (R)	AUC _{0-24,ss} (T) (n=30)	1880.98 (1747.06, 2025.16)	0.82 (0.78, 0.86)
		AUC _{0-24,ss} (R) (n=31)	2299.31 (2137.06, 2473.88)	
		C _{max,ss} (T) (n=30)	180.48 (167.68, 194.25)	0.50 (0.46, 0.54)
		C _{max,ss} (R) (n=31)	361.79 (336.67, 388.78)	

Note that the unites of AUC and C_{max} are h*pg/mL and pg/mL, respectively.

GMR: Geometric Mean Ratio.

Model: log-transformed PK parameter was analyzed separately by a mixed effects model with sequence, period and treatment as fixed effects and subject nested with in sequence as random effect.

For treatment QVA149 27.5/12.5 mcg x 2 BID, AUC_{0-24h,ss} PK parameter was derived by multiplying the AUC_{0-12h,ss} value by 2.

(Adapted from Table 11-5, 11-6, and 11-7 of Study QVA149A2107 report)

Conclusions

- The steady-state systemic exposure (AUC_{0-12h,ss}; C_{max,ss}) to indacaterol and glycopyrronium was similar after BID administration in FDC as QVA149 27.5/12.5 mcg (x 2) as compared to the BID administration of QAB149 27.5 mcg (x 2) alone or NVA237 12.5 mcg (x 2) alone respectively. There is no PK interaction between indacaterol and glycopyrronium when the FDC product QVA149 was administered.
- The relative bioavailability of indacaterol after BID administration in a FDC as QVA149 27.5/12.5 mcg compared to the QD administration of QAB149 75 mcg was estimated to be 0.82 (90% CI: 0.78, 0.86) based on the ratio of adjusted geometric means of AUC_{0-24h,ss}.

- The ratio of the geometric means and the corresponding 90% CI for $C_{max,ss}$ was 0.50 (90% CI: 0.46, 0.54) after inhalation of QVA149 27.5/12.5 mcg x 2 BID as compared to after inhalation of QAB149 75 mcg x 2 QD.

QT Study in HV

Study QVA149A2109

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

Objectives

Primary: To evaluate the effect of a single inhaled supratherapeutic dose of QVA149 (440 mcg indacaterol/400 mcg glycopyrronium) on the placebo- and baseline-corrected QTcF ($\Delta\Delta QTcF$) interval in HVs

Secondary:

- Safety and tolerability
- Effect of QVA149 on ECG parameters (heart rate, PR interval, QRS duration), absolute QTc values, PK, etc.
- Exposure-response relationship between the systemic exposure to indacaterol and glycopyrronium vs. the effect on the QTcF intervals after a single inhaled dose of QVA149 440/400 mcg in HVs

Study Design and Treatment Schedule: This is a randomized, partially-blinded, placebo and positive (moxifloxacin) controlled three period cross-over study to evaluate the effects of QVA149 on the corrected QT interval in HVs (Figure 13). 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 (indacaterol 440 mcg/400 mcg glycopyrronium), or matching placebo given in a double blind fashion, 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 for baseline (Baselines 2 and 3), dosing (~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.

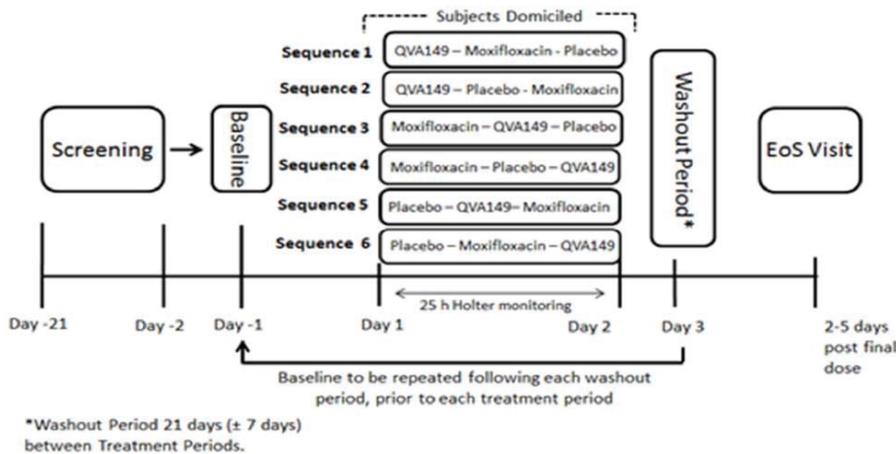


Figure 13. Study Design

(Source: Figure 9-1, Study QVA149A2109 report)

Table 36. Test Product

Study drug and strength	Formulation control number	Batch/Lot number
QVA149 (55 µg of indacaterol and 50 µg of glycopyrronium) capsules	6003019.002	X177FH (Batch number)
Placebo to QVA149 capsules	6001727.004	X090DI (Batch number)
Moxifloxacin 400 mg tablets	-	5402KLO (Lot number)

(Source: Table 9-1, Study QVA149A2109 report)

PD Assessment

Holter ECG recordings were recorded from 1 hour pre-dose to 24 hours post dose (-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) on the dosing day for each period. Up to ten 14-second replicates within the 5 minute extraction time window were taken to facilitate high precision QT analysis. QT interval (uncorrected), QTcF, HR, PR interval, QRS duration and RR interval were determined from these ECGs. The average of the replicate readings for each variable was used in the analysis.

PK Sampling Schedule

Blood samples were collected at 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.

Results

PD results

Primary PD results: The primary PD variable was the change from mean baseline in the QTcF interval, where mean baseline was the average of the -60, -45, -30, -15 and 0 (pre-dose) hour readings. The results of the analysis of QVA149 effects on QTcF are shown in Table 37 and are plotted in Figure 14. A mean baseline adjusted maximal difference between QVA149 and placebo ($\Delta\Delta\text{QTcF}$) of 9.18 ms was observed with an upper bound of the two-sided 90% CI of 10.46 ms at 30 minutes after dosing. The upper bound of the

two-sided 90% CI of the baseline adjusted mean difference between QVA149 and placebo in QTcF remained below 10ms at all other timepoints. The mean difference ($\Delta\Delta$ QTcF) exceeded 5ms for the period 0.25 to 1.5 hours after dosing.

Table 37. Treatment comparisons of change from baseline in QTcF interval by time-point for QVA149 versus Placebo

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)

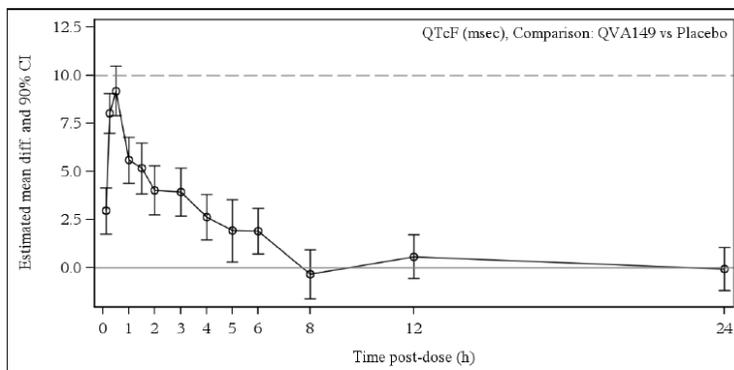
*: 0.117 h = 7 minutes

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: Table 14.2-1.1

((Source: Table 11-3, Study QVA149A2109 report)



Source: Figure 14.2-1.1

Figure 14. Estimated mean difference QVA149 versus placebo and 90% CI for change from baseline in QTcF interval by time-point and parameter

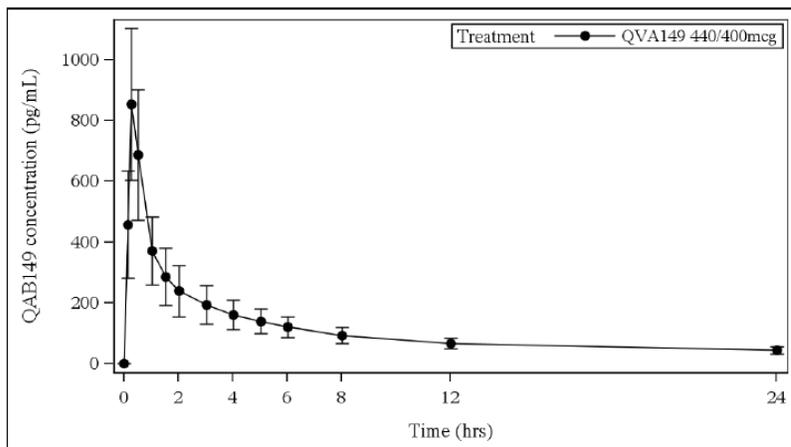
(Source: Figure 11-1, Study QVA149A2109 report)

PK results

Both indacaterol and glycopyrronium were systemically available shortly after QVA149 inhalation and plasma concentrations decreased rapidly thereafter. Median T_{max} was reached at 17 minutes after inhalation for indacaterol and 9 minutes after inhalation for glycopyrronium (Figure 15 and Table 38).

Compound: QVA149, Matrix: plasma, Analyte: QAB149

Linear view



Compound: QVA149, Matrix: plasma, Analyte: NVA237

Linear view

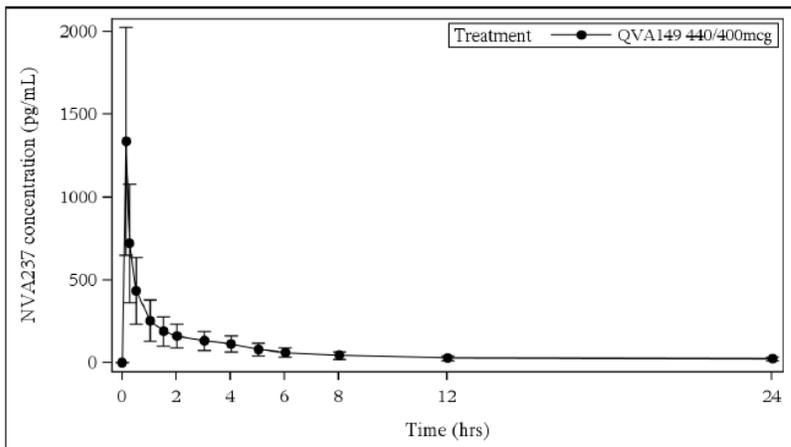


Figure 15. Arithmetic mean (SD) concentration-time profiles for QAB149 (upper panel) and NVA237 (lower panel)

(Adapted from Figures 11-3 and 11-4, Study QVA149A2109 report)

Table 38. Summary statistics of PK parameters by analyte and treatment

PK parameter (unit)	Analyte	
	QAB149	NVA237
AUClast (h*pg/mL)	2730 ± 738 (27.0%) [N=78]	1750 ± 748 (42.9%) [N=78]
Cmax (pg/mL)	854 ± 252 (29.5%) [N=78]	1330 ± 689 (51.9%) [N=78]
Tmax (h) [#]	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 Tmax, Statistics are median (min, max) [N]

Source: Table 14.2-2.2

(Source: Table 11-9, Study QVA149A2109 report)

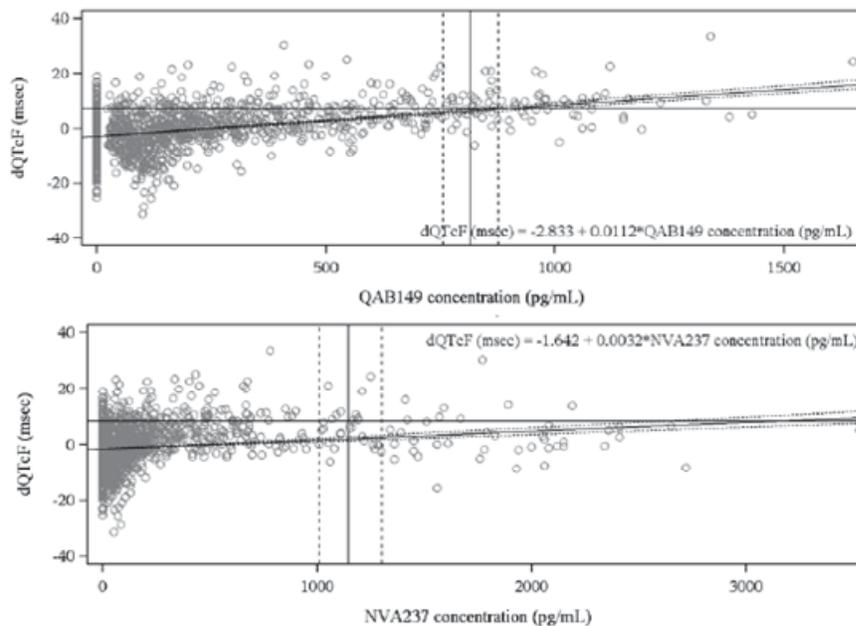
Exposure-response (PK/PD) relationship

The exposure-response relationship between the indacaterol and glycopyrronium plasma concentration and the corresponding change from baseline in QTcF showed that with

increasing concentrations of indacaterol and glycopyrronium, dQTcF tended to be increased slightly (Figures 16).

No relevant exposure-response relationship was observed between the systemic exposure to either indacaterol or glycopyrronium and changes in the uncorrected QT interval. Similarly, no relevant exposure-response relationship was observed between the systemic exposure to either indacaterol or glycopyrronium and the HR changes (Figures 17).

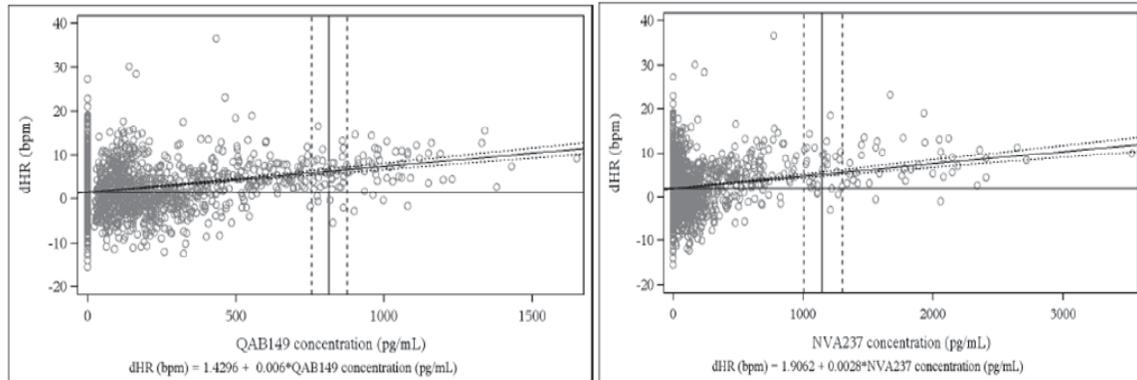
As the median Tmax was reached at 17 minutes after inhalation for indacaterol and 9 minutes after inhalation for glycopyrronium, it appears that the maximal plasma concentration of indacaterol are closer to the maximal effect observed on ddQTcF 30 minutes post inhalation. As QVA149 is a fixed-dose combination of QAB149 and NVA237, intrinsic effects of the individual components cannot be distinguished.



The solid regression line describes a linear relationship between QVA149 or 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.
The vertical lines are the geometric mean and 95% confidence limits for Cmax.

Figure 16. QAB149 plasma concentrations and corresponding change from baseline in QTcF

(Source: Adapted from Figures 11-5 and 11-6 of Study QVA149A2109 report)



The solid regression line describes the linear relationship between QAB149 or 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 the estimated intercept. The vertical lines are the geometric mean and 95% confidence limits for C_{max} .

Figure 17. QAB149 and NVA237 plasma concentrations and corresponding change from baseline in HR (dHR)

(Source: Adapted from Figures 11-7 and 11-8 of Study QVA149A2109 report)

Conclusions

- At estimated mean maximal $ddQTcF$ of 9.18 ms was observed at 30 minutes post-dose. The respective upper bound of the two-sided 90% CI was 10.46 ms. At all other time-points the upper confidence limit was below 10 ms.
- Small effects on QT-intervals were associated with high drug concentrations of indacaterol and glycopyrronium as shown by linear regression analysis of the concentration-QT relationship. Likely, the effect is mediated by the beta-2 agonist class-effects of indacaterol. However, since QVA149 is a fixed-dose combination of both indacaterol and glycopyrronium and the concentration peaks of both drugs were observed at similar time-points, intrinsic effects of either component cannot be distinguished.
- No relevant exposure-response relationship was observed between the exposure to either indacaterol or glycopyrronium and the changes in uncorrected QT. Similarly no relevant exposure-response relationship was observed between the exposure to either indacaterol or glycopyrronium and the HR changes.

For further details refer to QT/IRT review for NDA207930.

Dose Ranging Study in Asthma

Study QVA149A2210

Title: A multicenter, randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy, safety and tolerability of five different doses of inhaled indacaterol (QAB149) delivered via the single dose dry powder inhaler (SDDPI) in patients with persistent asthma

Objectives

Primary: to assess the acute (24-hour) bronchodilator effects of 5 different doses of indacaterol (27.5 mcg BID, 37.5 mcg QD, 55 mcg QD, 75 mcg QD, and 150 mcg QD) vs. placebo on FEV1 AUC(0-24h) in patients with asthma..

Secondary:

- To assess the bronchodilator effect on FEV1 AUC(0-12h), FEV1 AUC(12-24h); FEV1 peak effect; trough FEV1; and forced vital capacity (FVC)
- Safety and tolerability of indacaterol

Study Design and Treatment Schedule: This was a multicenter, double-blind, placebo-controlled, 6-period, 6-sequence crossover study (Figure 18). All study treatments were co-administered with background asthma controller therapy with fluticasone propionate. The study consisted of 3 epochs: Screening, Run-in, and a Treatment epoch consisting of 6 different 24 hour treatment periods which were separated by a wash-out phase of 14 days.

The study population consisted of adult male and female patients with a clinical diagnosis of persistent asthma who were on a stable treatment regimen with inhaled corticosteroids (ICS). Patients were randomly assigned through IRT to 1 of 6 treatment sequences, in a ratio of 1:1:1:1:1:1 with the aim that 15 patients were included in each sequence (Table 39). The study treatments consisted of 5 doses (27.5 mcg BID, 37.5 mcg QD, 55 mcg QD, 75 mcg QD, and 150 mcg QD) of indacaterol and matched placebo delivered via SDDPI.

Treatment Period	Screening	Run-in		Treatment Epoch																
				I	Wash out	II	Wash out	III	Wash out	IV	Wash out	V	Wash out	VI						
Visit	1	101	102	Randomization 201		202		203		204		205		299						
Treatment period day				1	2	1	2	1	2	1	2	1	2	1	2					
Study day	-21	-14 to 1		1	2	3-14	15	16	17-28	29	30	31-42	43	44	45-56	57	58	59-70	71	72
Study drug	Patients will receive a single dose of the following study drug on Day 1 of each treatment period (Visits 201, 202, 203, 204, 205, 299) Indacaterol 27.5 µg given as 2 inhalations via SDDPI Indacaterol 37.5 µg via SDDPI (and placebo capsules for indacaterol) or Indacaterol 55 µg via SDDPI (and placebo capsules for indacaterol) or Indacaterol 75 µg via SDDPI (and placebo capsules for indacaterol) or Indacaterol 150 µg via SDDPI (and placebo capsules for indacaterol) or Placebo via SDDPI All patients will be provided with albuterol for use as rescue medication throughout the study beginning at Visit 1 until the end of the treatment epoch All patients will be provided with fluticasone propionate 250 µg and be instructed to take b.i.d beginning at Visit 1 until end of the treatment epoch. There are 14 days of washout between Day 1 of each Treatment Period.																			

Figure 18. Study Design

(Source: Figure 9-1, Study QVA149A2210 report)

Table 39. Study treatment sequence

Treatment period	1	2	3	4	5	6
Sequence 1 (n=15)	A	B	F	C	E	D
Sequence 2 (n=15)	B	C	A	D	F	E
Sequence 3 (n=15)	C	D	B	E	A	F
Sequence 4 (n=15)	D	E	C	F	B	A
Sequence 5 (n=15)	E	F	D	A	C	B
Sequence 6 (n=15)	F	A	E	B	D	C

Treatment A: indacaterol 37.5 µg in the morning + matching placebo in the evening
 Treatment B: indacaterol 55 µg in the morning + matching placebo in the evening
 Treatment C: indacaterol 75 µg in the morning + matching placebo in the evening
 Treatment D: indacaterol 150 µg in the morning + matching placebo in the evening
 Treatment E: indacaterol 27.5 µg in the morning + indacaterol 27.5 µg in the evening
 Treatment F: placebo in the morning + placebo in the evening

(Source: Table 9-2, Study QVA149A2210 report)

Table 40. Test Product

Study drug and strength	Formulation control number	Batch number
Indacaterol 27.5 µg	6003518.004	X257 1112
Indacaterol 37.5 µg	6002886.006	X236 0513
Indacaterol 55 µg	6003519.003	X248 0613
Indacaterol 75 µg	6002142.008	X041AK
Indacaterol 150 µg	6002099.008	X291MH
Placebo	6001727.004	X090DI

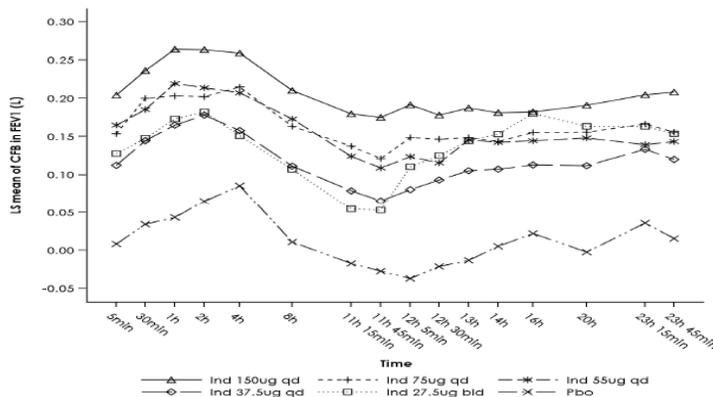
(Source: Table 9-1, Study QVA149A2210 report)

PK Sampling Schedule: No PK samples were collected in this study.

Results

Efficacy results:the 24-hour profile of LS means of change from period baseline in FEV₁ is presented in Figure 19 and the analysis for the change from period baseline in FEV₁ AUC(0-24h) is presented in Table 41. The estimated treatment differences from placebo and associated 95% CI of change from period baseline in FEV₁ AUC(0-24h) are presented in Figure 20.

All 5 indacaterol treatments showed statistically significant changes from period baseline in the acute bronchodilator effect i.e., change from period baseline in FEV₁ AUC(0-24h) compared to placebo (p<0.001), with LS mean differences vs. placebo ranging from 0.099 L to 0.187 L. The response profile of indacaterol 55 mcg QD and 75 mcg QD treatment was similar. Estimated treatment differences (with associated 95% CIs) of change from period baseline in FEV₁ AUC(0-24h) for indacaterol 37.5 mcg QD, 75 mcg QD and 150 mcg QD treatments were statistically significant compared to placebo and showed a dose-ordered response with clear separation of the dose strengths.



LMM: CFB in FEV₁ = treatment + period + overall mean baseline FEV₁ + period adjusted baseline correction + random effect of patient.

The overall mean baseline FEV₁ is the average of the 6 period baselines. Each period baseline FEV₁ is the mean of the -45 min and -15 min FEV₁ values taken on Day 1 prior to first dose in the respective period.

The period adjusted baseline correction is the deviation of a patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.

Source: Table 14.2-1.13.

Figure 19. 24-hour profile of change from period baseline in FEV₁

(Source: Figure 11-1, Study QVA149A2210 report)

Table 41. Change from period baseline in FEV1 (L) AUC(0-24h)

Treatment	n	Baseline Mean	CFB in FEV ₁ AUC LS Mean (SE)	Comparison	Treatment difference		
					LS Mean (SE)	(95% CI)	p-value
All	-	2.275	-	-	-	-	-
Ind 150 µg o.d.	84	2.243	0.209 (0.0153)	Ind 150 µg o.d. - Ind 75 µg o.d.	0.043 (0.0151)	(0.014, 0.073)	0.004
-	-	-	-	Ind 150 µg o.d. - Ind 37.5 µg o.d.	0.088 (0.0152)	(0.058, 0.118)	<0.001
-	-	-	-	Ind 150 µg o.d. - Pbo	0.187 (0.0151)	(0.157, 0.216)	<0.001
Ind 75 µg o.d.	86	2.277	0.165 (0.0152)	Ind 75 µg o.d. - Ind 55 µg o.d.	0.011 (0.0150)	(-0.018, 0.041)	-
-	-	-	-	Ind 75 µg o.d. - Ind 37.5 µg o.d.	0.045 (0.0150)	(0.015, 0.074)	0.003
-	-	-	-	Ind 75 µg o.d. - Ind 27.5 µg b.i.d.	0.022 (0.0150)	(-0.007, 0.051)	-
-	-	-	-	Ind 75 µg o.d. - Pbo	0.143 (0.0149)	(0.114, 0.173)	<0.001
Ind 55 µg o.d.	85	2.269	0.154 (0.0152)	Ind 55 µg o.d. - Pbo	0.132 (0.0150)	(0.103, 0.162)	<0.001
Ind 37.5 µg o.d.	84	2.282	0.121 (0.0153)	Ind 37.5 µg o.d. - Pbo	0.099 (0.0150)	(0.069, 0.128)	<0.001
Ind 27.5 µg b.i.d.	87	2.298	0.143 (0.0151)	Ind 27.5 µg b.i.d. - Pbo	0.121 (0.0150)	(0.092, 0.151)	<0.001
Pbo	86	2.279	0.022 (0.0152)	-	-	-	-

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from period baseline, - = not applicable.

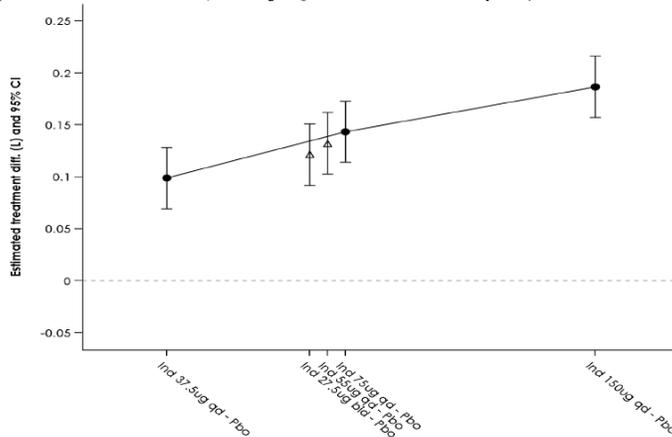
LMM: CFB in AUC = treatment + period + overall mean baseline FEV₁ + period adjusted baseline correction + random effect of patient.

The overall mean baseline FEV₁ is the average of the 6 period baselines. Each period baseline FEV₁ is the mean of the -45 min and -15 min FEV₁ values taken on Day 1 prior to first dose in the respective period.

The period adjusted baseline correction is the deviation of a patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.

Source: Table 14.2-1.1

(Source: Table 11-5, Study QVA149A2210 report)



LMM: CFB in AUC = treatment + period + overall mean baseline FEV₁ + period adjusted baseline correction + random effect of patient.

The overall mean baseline FEV₁ is the average of the 6 period baselines. Each period baseline FEV₁ is the mean of the -45 min and -15 min FEV₁ values taken on Day 1 prior to first dose in the respective period.

The period adjusted baseline correction is the deviation of a patient's period baseline for a given period from the overall mean baseline FEV₁ of the patient.

Source: Table 14.2-1.1.

Figure 20. FEV1 (L) AUC(0-24h) - treatment differences from placebo

(Source: Figure 11-2, Study QVA149A2210 report)

Conclusions

- No clinically meaningful difference in terms of the bronchodilator effect was observed for the indacaterol 55 mcg QD and the corresponding 27.5 mcg BID treatments, when compared with the indacaterol 75 mcg QD (Arcapta Neohaler) treatment.

- All 5 indacaterol treatments showed statistically significant changes from period baseline in terms of all secondary efficacy endpoints, compared to placebo.
- A dose-ordered response with statistically significant differences between dose levels was demonstrated for all the 37.5 mcg QD, 75 mcg QD, and 150 mcg QD indacaterol treatments.
- All indacaterol treatments were well-tolerated.

Phase 3 Efficacy and Safety Studies in COPD

Studies QVA149A2336 and A2337

The study design of Study QVA149A2336 and QVA149A2337 is identical.

Title: A 12-week treatment, multi-center, randomized, double-blind, parallel-group, placebo and active controlled study to assess the efficacy, safety, and tolerability of QVA149 (indacaterol maleate/glycopyrronium bromide) in COPD patients with moderate to severe airflow limitation.

Objectives

Primary: to demonstrate the superiority of QVA149 27.5/12.5 mcg BID compared to monotherapy components, QAB149 27.5 mcg BID and NVA237 12.5 mcg BID, in terms of standardized FEV1 AUC0-12h at Week 12.

Secondary:

- to demonstrate the superiority of QVA149 27.5/12.5 mcg BID compared to placebo at Week 12 in terms of the change in Health Status.
- To evaluate the superiority of QVA149 27.5/12.5 mcg BID, QAB149 27.5 mcg BID and NVA237 12.5 mcg BID compared to placebo in terms of standardized FEV1 AUC0-12h, trough FEV1, pre-dose trough FEV1 at Week 12, etc.
- to explore the PK of QAB149 and NVA237, either given as monotherapy (QAB149 27.5 mcg BID, NVA237 12.5 mcg BID) or fixed dose combination (QVA149 27.5/12.5 mcg BID) in a subset of patients using a population PK approach.

Study Design and Treatment Schedule: This study used a randomized, multi-center, double blind, placebo and active controlled, parallel group design to compare the efficacy and safety of QVA149 27.5/12.5 mcg BID vs. monotherapy components, QAB149 27.5 mcg BID and NVA237 12.5 mcg BID as well as placebo in COPD patients with moderate to severe airflow limitation. The study consisted of a screening epoch, a run-in epoch, a 12 week blinded treatment epoch, and a follow-up epoch of 30 days (Figure 21).

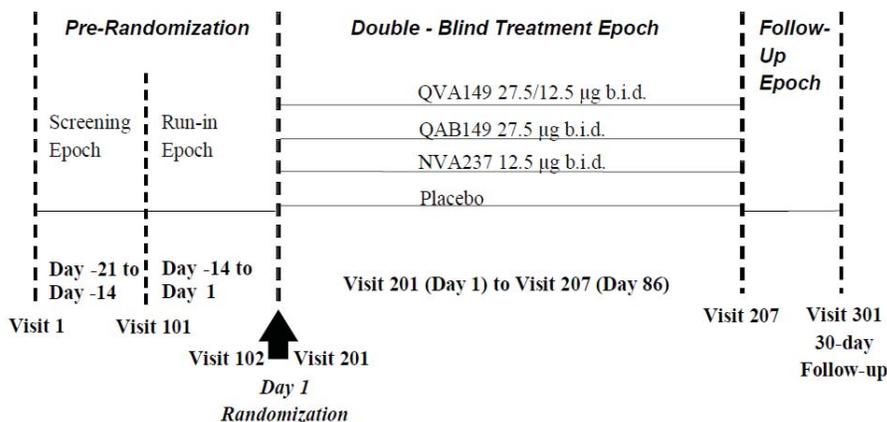


Figure 21. Study design of Studies QVA149A2336 and A2337
(Source: Figure 9-1, Studies QVA149A2336 and A2337 reports)

Table 42. Test Product in Study QVA149A2336

Study drug and strength	Formulation control number	Batch number
QVA149 27.5/12.5 µg capsules	6001565.006	X092DI
	6001565.007	X175HI
QAB149 27.5 µg capsules	6003518.004	X1130512
	6003518.004	X115 0512
	6003518.004	X1170512
	6003518.004	X257 1112
	6003518.004	X258 1112
NVA237 12.5 µg capsules	6002278.007	X097DI
	6002278.011	X098EI
	6002278.015	X099EI
Placebo capsules	6001727.004	X090DI
	6001727.004	X124CH

(Source: Table 9-1, Study QVA149A2336)

Table 43. Test Product in Study QVA149A2337

Study drug and strength	Formulation control number	Batch number
QVA149 27.5/12.5 µg capsules	6001565	X092DI
	6001565	X175HI
NVA237 12.5 µg capsules	6002278	X098EI
	6002278	X097DI
	6002278	X099EI
QAB149 27.5 µg capsules	6003518	X1130512
	6003518	X114 0512
	6003518	X116 0512
	6003518	X259 1212
Placebo capsules	6001727	X090DI
	6001727	X124CH

(Source: Table 9-1, Study QVA149A2337)

PK Sampling Schedule: In a subset of patients who gave consent for this optional sampling, PK blood samples were planned to be collected in approximately 20% of randomized patients at 25 min pre-dose and at 4 time points post-dose (2 min, 20 min, 55 min, and 3 hours 50 min) at Day 29 and Day 85 at selected clinical centers.

PK data will be used for population PK analysis.

Efficacy Results

The primary efficacy objective was to demonstrate the superiority of QVA149 27.5/12.5 mcg

BID compared to the monotherapy components, QAB149 27.5 mcg BID and NVA237 12.5 mcg BID, in terms of standardized FEV1 AUC(0-12h) at Week 12. The superiority of QVA149 vs. the monotherapy components (QAB149 and NVA237) in terms of change from baseline in FEV1 AUC(0-12h) at Day 85, was achieved and the differences were statistically significant ($p < 0.001$ for both) (Table 44).

QVA149 had a significant bronchodilator effect after the first dose at 5 min on Day 1. Even after 12 weeks of treatment, the effect on lung function (FEV1) remained highest for QVA149 compared to QAB149 and NVA237 and placebo up to 11 h 55 min post-dose (Figure 22). There was a clear separation of the FEV1 time profile curve of QVA149 27.5/12.5 mcg BID from the monotherapy curves and placebo.

Table 44. Improvement of airflow obstruction (FEV1 AUC(0-12h) at Day 85) - (QVA149A2337, QVA149A2336, and pooled analysis)

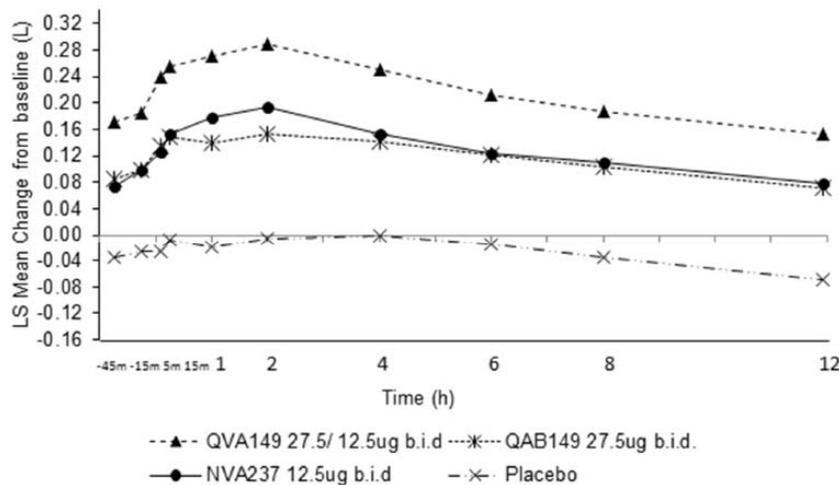
Component	Statistic	Treatment difference in change from baseline for FEV ₁ (L) AUC _(0-12h) at Day 85		
		Study A2337	Study A2336	Pooled analysis
Primary Objective				
QAB149 monotherapy component (QVA149 – NVA237)	LS mean	0.079	0.098	0.088
	95% CI	(0.042; 0.116)	(0.059; 0.137)	(0.061; 0.115)
	p-value	<0.001	<0.001	<0.001
NVA237 monotherapy component (QVA149 – QAB149)	LS mean	0.112	0.094	0.103
	95% CI	(0.075; 0.149)	(0.055; 0.133)	(0.076; 0.130)
	p-value	<0.001	<0.001	<0.001
Comparison to placebo				
QVA149 (combination) (QVA149 – Placebo)	LS mean	0.262	0.231	0.246
	95% CI	(0.224; 0.300)	(0.192; 0.271)	(0.219; 0.274)
	p-value	<0.001	<0.001	<0.001

AUC_(0-12h) = area under the curve of plasma concentration from 0 to 12 h; CI = confidence interval; FEV₁ = forced expiratory volume in 1 sec; LS Mean = least squares mean.

All LS Means, CIs, and p-values are from a MMRM: change from baseline in FEV₁ AUC = treatment + baseline FEV₁ + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV₁*visit interaction + region. The model for the pooled analysis also contained the term for study, and interaction terms for study*treatment, study*visit, and study*treatment*visit. Baseline FEV₁ is defined as the average of the -45 min and -15 min FEV₁ values taken on Day 1.

Source: [SCE-Table 3-20 and Table 3-47]

(Source: Table 4-4, Clinical Overview)



b.i.d. = twice daily; LS mean = least squares mean; FEV₁ = forced expiratory volume in 1 sec. Baseline is defined as the average of the pre-dose FEV₁ measured at -45 min and -15 min at Day 1.

Source: [SCE-Figure 3-10]

Figure 22. Profile of change from baseline in FEV1 (L) from 5 min up to 11 h

55 min post-dose on Day 85 (pooled analysis of Studies QVA149A2336 and A2337)
(Source: Figure 4-3, Clinical Overview)

Conclusions

- QVA149 27.5/12.5 mcg BID provided significantly superior and clinically meaningful improvements in lung function vs QAB149 27.5 mcg BID and NVA237 12.5 mcg BID, in patients with moderate to severe COPD.

For more details regarding efficacy and safety of QVA149 27.5/12.5 mcg BID, refer to Clinical Review.

• 4.3. Appendix – New Drug Application Filing and Review Form

CLINICAL PHARMACOLOGY FILING FORM			
Application Information			
NDA/BLA Number	207930	SDN	
Applicant	Novartis	Submission Date	12/29/2014
Generic Name	Indacaterol/Glycopyrrolate	Brand Name	
Drug Class	Indacaterol: Long-acting β 2-adrenergic agonist Glycopyrrolate: Long-acting muscarinic antagonist		
Indication	Chronic obstructive Pulmonary Disease		
Dosage Regimen	27.5/12.5 μ g, BID		
Dosage Form	Powder for inhalation	Route of Administration	Inhalation
OCP Division	DCP II	OND Division	OND Division II
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Lei He, PhD	Satjit Brar, Pharm.D., PhD	
Pharmacometrics	Lei He, PhD	Liang Zhao, PhD	
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	2/27/2015	74-Day Letter Date	3/13/2015
Review Due Date	9/24/2015	PDUFA Goal Date	10/29/2015
Application Fileability			
Is the Clinical Pharmacology section of the application fileable? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes list comment(s)			
Is there a need for clinical trial(s) inspection? <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No Clinical Pharmacology <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No			

Studies Bioanalytical and Analytical Methods		<input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Summary Labeling	No <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Clinical Pharmacology Studies				
Study Type	Count	Comment(s)		
In Vitro Studies				
<input checked="" type="checkbox"/> Metabolism Characterization	1	DMPK R1100757		
<input type="checkbox"/> Transporter Characterization				
<input type="checkbox"/> Distribution				
<input checked="" type="checkbox"/> Drug-Drug Interaction	5	DMPK R1200049, DMPK R1200048, DMPK R1100624, DMPK R1100625, DMPK R1100671		
In Vivo Studies				
Biopharmaceutics				
<input type="checkbox"/> Absolute Bioavailability				
<input type="checkbox"/> Relative Bioavailability				
<input checked="" type="checkbox"/> Bioequivalence	4	CQVA149A2101, CQVA149A2103, CQVA149A2106, CQVA149A2107		
<input type="checkbox"/> Food Effect				
<input type="checkbox"/> Other				
Human Pharmacokinetics				
Healthy Subjects	<input type="checkbox"/> Single Dose			
	<input type="checkbox"/> Multiple Dose			
Patients	<input type="checkbox"/> Single Dose			
	<input type="checkbox"/> Multiple Dose			
<input type="checkbox"/> Mass Balance Study				
<input type="checkbox"/> Other (e.g. dose proportionality)				
Intrinsic Factors				
<input checked="" type="checkbox"/> Race	2	CQVA149A1101, CQVA149A2104		
<input type="checkbox"/> Sex				
<input type="checkbox"/> Geriatrics				
<input type="checkbox"/> Pediatrics				
<input type="checkbox"/> Hepatic Impairment				
<input type="checkbox"/> Renal Impairment				
<input type="checkbox"/> Genetics				

Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
Pharmacokinetics/Pharmacodynamics			
<input checked="" type="checkbox"/> Healthy Subjects	1	CQVA149A2105	
<input checked="" type="checkbox"/> Patients	4	QVA149A2210, QVA149A2336, QVA149A2337, CQVA149A2204	
<input checked="" type="checkbox"/> QT	1	CQVA149A2109	
Pharmacometrics			
<input checked="" type="checkbox"/> Population Pharmacokinetics	2	PopPK QVA149 27.5 12.5 ug b.i.d CQVA149A2303-population-pk	
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed		6	14

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	The to-be-marketed product was used in the pivotal clinical trial.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?		
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
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8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Filing Memo

This is optional, discuss with your TL content and format

Regulatory History

QVA149 (indacaterol/glycopyrrolate) is a fixed-dose combination (FDC) of QAB149 (indacaterol, a long-acting β 2-adrenergic agonist (LABA)) and NVA237 (glycopyrrolate, a long-acting muscarinic antagonist (LAMA)). It was proposed for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The combination product is formulated as a dry powder in hard capsules that are inserted into a single dose, dry powder inhalation device (Concept1).

The individual monotherapy components, indacaterol (QAB149) and glycopyrrolate (NVA237) have also been developed for the treatment of COPD:

- QAB149 (Arcapta[®] Neohaler[®], NDA 22383) 75 μ g once daily (q.d.) was approved in the US in 2011 for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It was first approved in 2009 in the European Union (EU) and is currently approved in over 100 countries.
- NVA237 (Seebri[™] Neohaler[®], NDA 207923) 12.5 μ g twice daily (b.i.d.) is intended for the long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. (b) (4)

The development of QVA149 FDC product was consistent with the regulatory advice in the NVA237 registration program under NDA207923 regarding dose selection. Novartis originally proposed (b) (4)

(b) (4) for the US FDA submission.

In IND48655 (NVA237) end-of-Phase 2 meeting (July 15, 2008) and pre-NDA meeting (September 28, 2011), FDA disagreed the proposed dosing regimen (b) (4)

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Clinical Pharmacology Studies

The relevant clinical pharmacology studies submitted under NDA 207930 were summarized in Table 1.

Table1. Summary of Relevant Clinical Pharmacology Studies

	Study ID	Study Design	Objectives	Treatments
Comparative BA/BE study in HV	CQVA149A2101	OL, R, SD, crossover, N=28	Safety, PK	QAB 300 µg, Concept 1 NVA 100 µg, Concept 1 QVA 300/100 µg, Concept 1
	CQVA149A2103	OL, R, crossover, MD, N=42	Safety, PK	QAB 150 µg, QD, Concept 1 NVA 50 µg, QD, Concept 1 QVA 150/50 µg, QD, Concept 1
	CQVA149A2106	OL, R, crossover, MD, N=24	Safety, PK	QAB 150 µg, QD, Concept 1 NVA 50 µg, QD, Concept 1 QVA 150/50 µg, free combination, QD, Concept 1
	CQVA149A2107	OL, R, crossover, MD, N=36	PK interaction, safety	QAB 27.5µg×2, BID, Concept 1 QAB 75µg×2, QD, Concept 1 NVA 12.5µg×2, BID, Concept 1 QVA 27.5/12,5µg×2, BID, Concept 1
Intrinsic factor PK study	CQVA149A1101	R, DB, placebo-controlled, SD, in Caucasian and Japanese, N=48	Safety, PK	QVA 110/50 µg, Concept 1 QVA 220/100 µg, Concept 1
	CQVA149A2104	OL, MD, in Chinese, N=12	PK, safety	QVA 110/50 µg, QD, Concept 1

PD, PK/PD study in HV	CQVA149A2105	DB, R, placebo/active drug controlled, incomplete crossover, SD, N=56	PD, safety, PK	QVA 440/200 µg, Concept 1 QAB 600 µg, Concept 1 NVA 200 µg, Concept 1 Salmeterol 200 µg, Concept 1 Placebo
	CQVA149A2109	R, partially blinded, placebo/positive controlled, crossover, SD, N=84	PD (The effect of QVA on QT interval in HV), safety, PK	QVA 55/50 µg Moxifloxacin, 400 mg, oral Placebo
PD, PK/PD in asthma patient	QVA149A2210	R, DB, placebo controlled, crossover, MD, in patients with asthma, N=91	Indacaterol dose ranging, efficacy, PK	QAB 37.5 µg, QD QAB 55 µg, QD QAB 75 µg, QD QAB 150 µg, QD QAB 27.5 µg, BID
Efficacy and safety study in COPD patients	QVA149A2336	R, DB, parallel, placebo/active controlled, MD, in COPD, N=1042	Efficacy, safety, PK, PG	QVA 27.5/12,5µg, BID QAB 27.5 µg, BID NVA 12.5µg, BID Placebo
	QVA149A2337	R, DB, parallel, placebo/active controlled, MD, in COPD, N=1001	Efficacy, safety, PK, PG	QVA 27.5/12,5µg, BID QAB 27.5 µg, BID NVA 12.5µg, BID Placebo

*BA: bioavailability; BE: bioequivalence; HV: healthy volunteer; OL: open label; R: randomized; DB: double-blind; SD: single dose; NVA: NVA237; QAB: QAB149; QVA: QVA 149; Concept 1: Concept 1 inhalation device; PG: pharmacogenetics; SDDPI: single dose dry powder inhaler; FDC: fixed-dose combination

Dose and Dose Regimen Selection

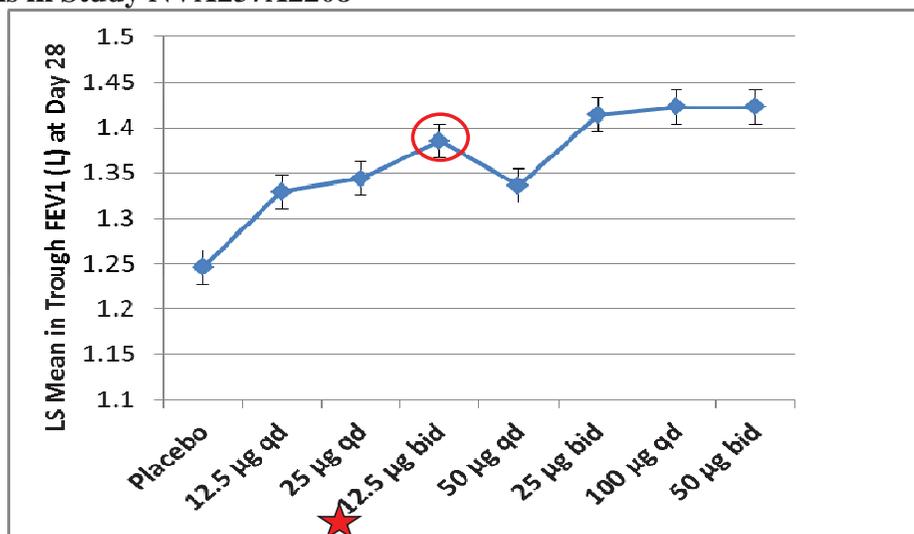
NVA237 (glycopyrrolate)

The dose regimen of NVA237 was identified in two studies: Study NVA237A2205 and Study NVA237A2208.

Study NVA237A2205 was a randomized, double-blind, placebo-controlled, 4 period incomplete crossover dose-ranging study in stable COPD patients to assess the efficacy and safety of 4 doses of NVA237, including NVA237 12.5 µg QD, 25 µg QD, 50 µg QD, and 100 µg QD. The treatment difference (NVA237 vs. placebo) for trough FEV1 on Day 7 were dose-ordered, ranging from 0.075 L (12.5 µg QD) to 0.142 L (100 µg QD). Following discussion with the FDA, an additional dose ranging study, Study NVA237A2208 was conducted. Study NVA237A2208 was a randomized, double-blind,

placebo-controlled, 2-period, crossover study to assess the efficacy and safety of different doses of NVA237 administered either once daily or twice daily to severe COPD patients. The tested dose regimens included NVA237 12.5 µg QD, 25 µg QD, 12.5 µg BID, 50 µg QD, 25 µg BID, 100 µg QD, and 50 µg BID. According to the data analysis, on Day 28, all NVA237 doses had significant higher mean trough FEV1 when compared to placebo. NVA237 12.5 µg BID was found to be the lowest dose with a clinically important (>0.100 L) difference compared to placebo (0.139 L) and therefore was selected as the NVA237 dose regimen to support the NDA207923 and NDA207930 submissions (Figure 1).

Figure 1. The LS mean in trough FEV1 (L) at Day 28 following different dosing regimens in Study NVA237A2208

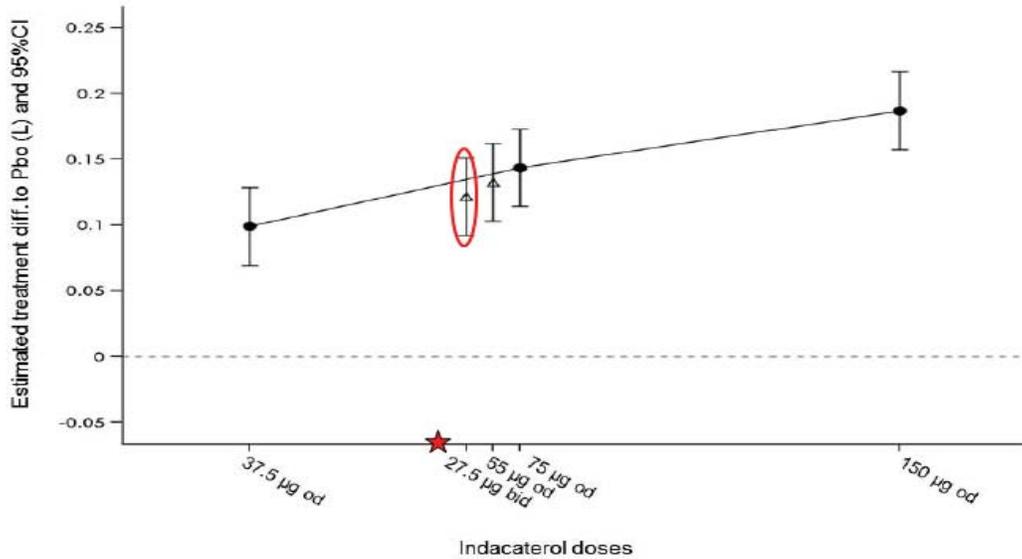


QAB149 (indacaterol)

The development program of QVA149 was consistent with the regulatory advice in NVA237 registration program regarding dose selection. With the agreement of dose selection for NVA237, 12.5 µg BID, [REDACTED] (b) (4).

Study QVA149A2210 was a multi-center, double-blind, placebo-controlled, crossover study in patients with persistent asthma. All study treatments were co-administered with patients being on background asthma controller therapy. The primary objective of this study was to assess the acute (24-h) bronchodilator effects of 5 different doses of QAB149 27.5 µg BID, 37.5 µg QD, 55 µg QD, 75 µg QD, and 150 µg QD on FEV1 AUC(0-24h). Results indicated all 5 QAB149 doses showed statistically significant improvements in both primary and secondary endpoints vs. placebo, and 27.5 µg BID was selected as QAB149 dose regimen in QVA149 FDC product (Figure 2).

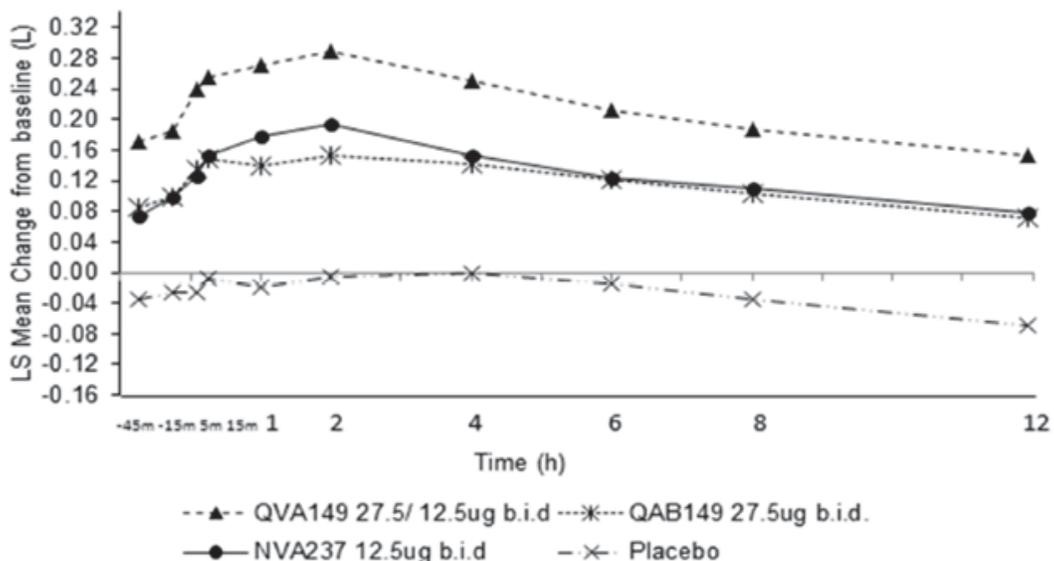
Figure 2. FEV1 (L) AUC_(0-24h)-treatment differences from indacaterol to placebo in Study QVA149A2210



QVA 149 (indacaterol/glycopyrrolate)

27.5/12.5 µg, BID was proposed as the dose regimen for QVA149. Two pivotal efficacy studies, Study QVA149A2336 and Study QVA149A2337, compared the efficacy and safety of QVA149 vs. its monotherapy components and placebo over 12 weeks of treatment in COPD patients with moderate and server airflow limitation. The pooled data analysis indicated QVA149 27.5/12.5 µg, BID provided clinically meaningful improvement in lung function in COPD patients compared with each monotherapy (Figure 3).

Figure 3. Profile of change from baseline in FEV1 (L) from 5 min up to 11 h 55 min post-dose on Day 85 (pooled analysis)



Summary of NVA237 and QAB149 PK

The PK characteristics of NVA237 and QAB149 are summarized in Table 2.

NVA237 (glycopyrrolate)

Following oral inhalation of QVA149 via the Concept 1 device, the absolute bioavailability of glycopyrrolate is estimated to be about 40% and the peak plasma level can be reached at 5 min. After inhalation, the mean terminal half-life of glycopyrrolate is 33-57h, which is much longer than half-lives of 6.2 h and 2.8 h following IV and oral administration, respectively. *In vitro* human plasma protein binding of glycopyrrolate was 38-41% at concentrations of 1-10 ng/mL. *In vitro* metabolism studies showed consistent metabolic pathways between animals and humans. Renal elimination of parent drug accounts for about 60-70% of total clearance of systemically available glycopyrrolate whereas non-renal clearance accounts for about 30-40%. The PK of glycopyrrolate following inhalation of NVA237 is linear and dose proportional in COPD patients. Since the drug effect is achieved topically in the lungs, food is not expected to affect lung deposition.

QAB149 (indacaterol)

Following oral inhalation of QVA149 via the Concept 1 device, the absolute bioavailability of indacaterol is estimated to be about 45% and the peak plasma level can be reached at 15 min. *In vitro* human serum and plasma protein binding of indacaterol is high, ranging from 94.1 to 95.3% and 95.1 to 96.2 % respectively. *In vitro* studies showed that the predominant enzymes responsible for the metabolism of indacaterol are UGT1A1 and CYP3A4. Indacaterol is a low affinity substrate for P-gp. Fecal route is the dominant route of excretion. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and hydroxylated metabolites (23% of the dose). The amount of unchanged indacaterol in urine is generally less than 2% of the dose. Since the drug effect is achieved topically in the lungs, food is not expected to affect lung deposition.

Table 2. PK characteristics of NVA237 and QAB149

	NVA237 (Glycopyrrolate)	QAB149 (Indacaterol)
Tmax	5 min	15 min
Bioavailability	40%	45%
Protein binding	Plasma: 38-41%	Serum: 94.1-95.3% Plasma: 95.1-96.2%
T1/2	33-57 hrs	45.5 -126 hrs
Linear PK	50 - 200 µg	150 - 600 µg
Metabolism	Minor	UGT1A1 and CYP3A4
Elimination	Renal 60-70%, Non-renal 30-40% Mostly parent	Fecal 70-80% Renal <2% Mostly parent
Food effect	Minimal	Minimal

PK Interaction between NVA237 and QAB149

The PK interaction between glycopyrrolate and indacaterol was investigated in Study QVA149A2107. It was an open-label, randomized, non-confirmatory, 4-period crossover study to assess and compare the systemic exposure of glycopyrrolate and indacaterol after administration of QVA149 27.5/12.5 µg ×2 BID, QAB 27.5 µg ×2 BID, and NVA237 12.5 µg ×2 BID. Results indicated that, following the administration of QVA149, the steady-state systemic exposure (AUC_{0-12h, ss}, and C_{max,ss}) to each component was similar as compared to that following each of the monotherapies (Table 3). Therefore, there is no PK interaction between NVA237 and QAB149.

Table 3. Comparison of systemic exposure of indacaterol and glycopyrrolate following the administration of QVA149 or monotherapies

Treatment	Parameter	GMR (90% CI)
QVA149 bid vs. QAB149 bid (FDC) (Mono)	AUCt	0.95 (0.91, 0.99)
	C _{max}	0.97 (0.93, 1.02)
QVA149 bid vs. NVA237 bid (FDC) (Mono)	AUCt	1.09 (1.05, 1.13)
	C _{max}	1.07 (0.97, 1.18)

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

/s/

LEI HE
09/24/2015

DINKO REKIC
09/24/2015

YANING WANG
09/24/2015

SURESH DODDAPANENI
09/24/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	207930	SDN	
Applicant	Novartis	Submission Date	12/29/2014
Generic Name	Indacaterol/Glycopyrrolate	Brand Name	
Drug Class	Indacaterol: Long-acting β 2-adrenergic agonist Glycopyrrolate: Long-acting muscarinic antagonist		
Indication	Chronic obstructive Pulmonary Disease		
Dosage Regimen	27.5/12.5 μ g, BID		
Dosage Form	Powder for inhalation	Route of Administration	Inhalation
OCP Division	DCP II	OND Division	OND Division II
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Lei He, PhD	Satjit Brar, Pharm D, PhD	
Pharmacometrics	Lei He, PhD	Liang Zhao, PhD	
Genomics			
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	2/27/2015	74-Day Letter Date	3/13/2015
Review Due Date	9/24/2015	PDUFA Goal Date	10/29/2015
Application Fileability			
Is the Clinical Pharmacology section of the application fileable?			
<input checked="" type="checkbox"/> Yes			
<input type="checkbox"/> No			
If no list reason(s)			
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
If yes list comment(s)			
Is there a need for clinical trial(s) inspection?			
<input type="checkbox"/> Yes			
<input checked="" type="checkbox"/> No			
If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary
Bioanalytical and Analytical Methods		<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Labeling
			<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Clinical Pharmacology Studies			
Study Type	Count	Comment(s)	
In Vitro Studies			
<input checked="" type="checkbox"/> Metabolism Characterization	1	DMPK R1100757	
<input type="checkbox"/> Transporter Characterization			
<input type="checkbox"/> Distribution			
<input checked="" type="checkbox"/> Drug-Drug Interaction	5	DMPK R1200049, DMPK R1200048, DMPK R1100624, DMPK R1100625, DMPK R1100671	

In Vivo Studies			
Biopharmaceutics			
<input type="checkbox"/> Absolute Bioavailability			
<input type="checkbox"/> Relative Bioavailability			
<input checked="" type="checkbox"/> Bioequivalence	4	CQVA149A2101, CQVA149A2103, CQVA149A2106, CQVA149A2107	
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input checked="" type="checkbox"/> Race	2	CQVA149A1101, CQVA149A2104	
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
Pharmacokinetics/Pharmacodynamics			
<input checked="" type="checkbox"/> Healthy Subjects	1	CQVA149A2105	
<input checked="" type="checkbox"/> Patients	4	QVA149A2210, QVA149A2336, QVA149A2337, CQVA149A2204	
<input checked="" type="checkbox"/> QT	1	CQVA149A2109	
Pharmacometrics			
<input checked="" type="checkbox"/> Population Pharmacokinetics	2	PopPK QVA149 27.5 12.5 ug b.i.d CQVA149A2303-population-pk	
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed		6	14

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	The to-be-marketed product was used in the pivotal clinical trial.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

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[REDACTED] for the US FDA submission.

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PD, PK/PD in asthma patient	QVA149A2210	R, DB, placebo controlled, crossover, MD, in patients with asthma, N=91	Indacaterol dose ranging, efficacy, PK	QAB 37.5 µg, QD QAB 55 µg, QD QAB 75 µg, QD QAB 150 µg, QD QAB 27.5 µg, BID
Efficacy and safety study in COPD patients	QVA149A2336	R, DB, parallel, placebo/active controlled, MD, in COPD, N=1042	Efficacy, safety, PK, PG	QVA 27.5/12,5µg, BID QAB 27.5 µg, BID NVA 12.5µg, BID Placebo
	QVA149A2337	R, DB, parallel, placebo/active controlled, MD, in COPD, N=1001	Efficacy, safety, PK, PG	QVA 27.5/12,5µg, BID QAB 27.5 µg, BID NVA 12.5µg, BID Placebo

*BA: bioavailability; BE: bioequivalence; HV: healthy volunteer; OL: open label; R: randomized; DB: double-blind; SD: single dose; NVA: NVA237; QAB: QAB149; QVA: QVA 149; Concept 1: Concept 1 inhalation device; PG: pharmacogenetics; SDDPI: single dose dry powder inhaler; FDC: fixed-dose combination

Dose and Dose Regimen Selection

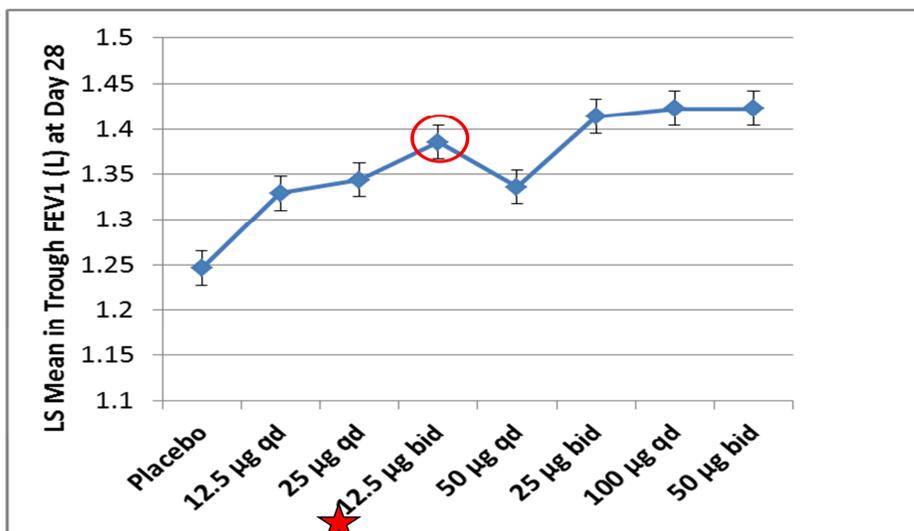
NVA237 (glycopyrrolate)

The dose regimen of NVA237 was identified in two studies: Study NVA237A2205 and Study NVA237A2208.

Study NVA237A2205 was a randomized, double-blind, placebo-controlled, 4 period incomplete crossover dose-ranging study in stable COPD patients to assess the efficacy and safety of 4 doses of NVA237, including NVA237 12.5 µg QD, 25 µg QD, 50 µg QD, and 100 µg QD. The treatment difference (NVA237 vs. placebo) for trough FEV1 on Day 7 were dose-ordered, ranging from 0.075 L (12.5 µg QD) to 0.142 L (100 µg QD).

Following discussion with the FDA, an additional dose ranging study, Study NVA237A2208 was conducted. Study NVA237A2208 was a randomized, double-blind, placebo-controlled, 2-period, crossover study to assess the efficacy and safety of different doses of NVA237 administered either once daily or twice daily to severe COPD patients. The tested dose regimens included NVA237 12.5 µg QD, 25 µg QD, 12.5 µg BID, 50 µg QD, 25 µg BID, 100 µg QD, and 50 µg BID. According to the data analysis, on Day 28, all NVA237 doses had significant higher mean trough FEV1 when compared to placebo. NVA237 12.5 µg BID was found to be the lowest dose with a clinically important (>0.100 L) difference compared to placebo (0.139 L) and therefore was selected as the NVA237 dose regimen to support the NDA207923 and NDA207930 submissions (Figure 1).

Figure 1. The LS mean in trough FEV1 (L) at Day 28 following different dosing regimens in Study NVA237A2208



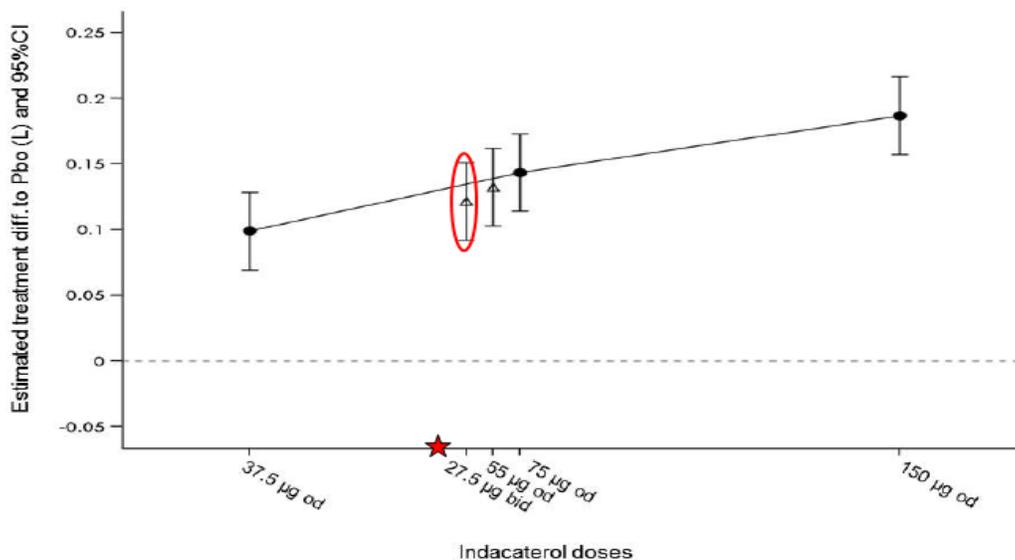
QAB149 (indacaterol)

The development program of QVA149 was consistent with the regulatory advice in NVA237 registration program regarding dose selection. With the agreement of dose selection for NVA237, 12.5 µg (b) (4)

Study QVA149A2210 was a multi-center, double-blind, placebo-controlled, crossover study in patients with persistent asthma. All study treatments were co-administered with patients being on background asthma

controller therapy. The primary objective of this study was to assess the acute (24-h) bronchodilator effects of 5 different doses of QAB149 27.5 µg BID, 37.5 µg QD, 55 µg QD, 75 µg QD, and 150 µg QD on FEV1 AUC(0-24h). Results indicated all 5 QAB149 doses showed statistically significant improvements in both primary and secondary endpoints vs. placebo, and 27.5 µg BID was selected as QAB149 dose regimen in QVA149 FDC product (Figure 2).

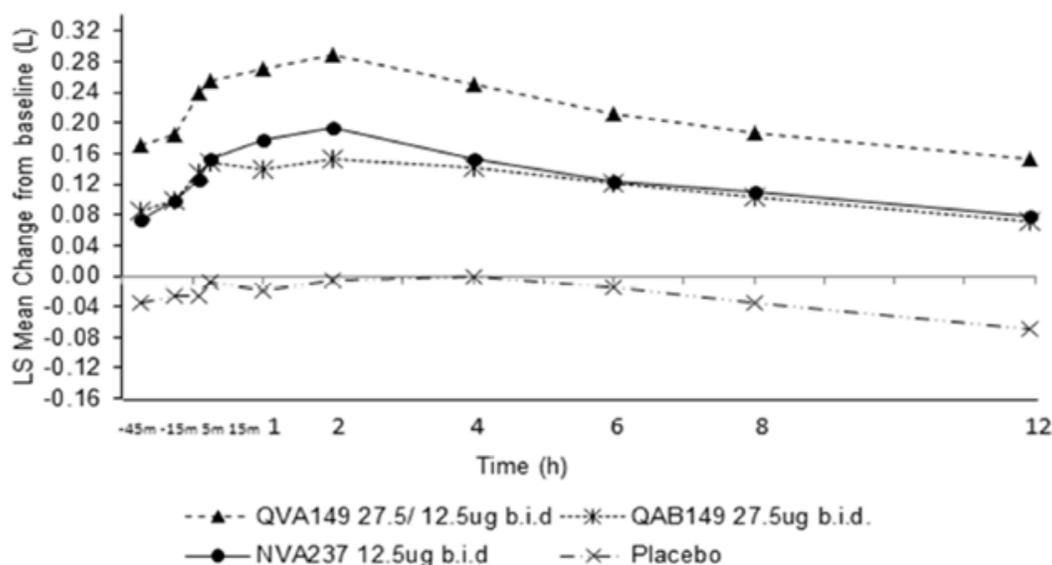
Figure 2. FEV1 (L) AUC_(0-24h)-treatment differences from indacaterol to placebo in Study QVA149A2210



QVA 149 (indacaterol/glycopyrrolate)

27.5/12.5 µg, BID was proposed as the dose regimen for QVA149. Two pivotal efficacy studies, Study QVA149A2336 and Study QVA149A2337, compared the efficacy and safety of QVA149 vs. its monotherapy components and placebo over 12 weeks of treatment in COPD patients with moderate and server airflow limitation. The pooled data analysis indicated QVA149 27.5/12.5 µg, BID provided clinically meaningful improvement in lung function in COPD patients compared with each monotherapy (Figure 3).

Figure 3. Profile of change from baseline in FEV1 (L) from 5 min up to 11 h 55 min post-dose on Day 85 (pooled analysis)



Summary of NVA237 and QAB149 PK

The PK characteristics of NVA237 and QAB149 are summarized in Table 2.

NVA237 (glycopyrrolate)

Following oral inhalation of QVA149 via the Concept 1 device, the absolute bioavailability of glycopyrrolate is estimated to be about 40% and the peak plasma level can be reached at 5 min. After inhalation, the mean terminal half-life of glycopyrrolate is 33-57h, which is much longer than half-lives of 6.2 h and 2.8 h following IV and oral administration, respectively. *In vitro* human plasma protein binding of glycopyrrolate was 38-41% at concentrations of 1-10 ng/mL. *In vitro* metabolism studies showed consistent metabolic pathways between animals and humans. Renal elimination of parent drug accounts for about 60-70% of total clearance of systemically available glycopyrrolate whereas non-renal clearance accounts for about 30-40%. The PK of glycopyrrolate following inhalation of NVA237 is linear and dose proportional in COPD patients. Since the drug effect is achieved topically in the lungs, food is not expected to affect lung deposition.

QAB149 (indacaterol)

Following oral inhalation of QVA149 via the Concept 1 device, the absolute bioavailability of indacaterol is estimated to be about 45% and the peak plasma level can be reached at 15 min. *In vitro* human serum and plasma protein binding of indacaterol is high, ranging from 94.1 to 95.3% and 95.1 to 96.2 % respectively. *In vitro* studies showed that the predominant enzymes responsible for the metabolism of indacaterol are UGT1A1 and CYP3A4. Indacaterol is a low affinity substrate for P-gp. Fecal route is the dominant route of excretion. Indacaterol was excreted into human feces primarily as unchanged parent drug (54% of the dose) and hydroxylated metabolites (23% of the dose). The amount of unchanged indacaterol in urine is generally less than 2% of the dose. Since the drug effect is achieved topically in the lungs, food is not expected to affect lung deposition.

Table 2. PK characteristics of NVA237 and QAB149

	NVA237 (Glycopyrrolate)	QAB149 (Indacaterol)
Tmax	5 min	15 min
Bioavailability	40%	45%
Protein binding	Plasma: 38-41%	Serum: 94.1-95.3% Plasma: 95.1-96.2%
T1/2	33-57 hrs	45.5 -126 hrs
Linear PK	50 - 200 µg	150 - 600 µg
Metabolism	Minor	UGT1A1 and CYP3A4
Elimination	Renal 60-70%, Non-renal 30-40% Mostly parent	Fecal 70-80% Renal <2% Mostly parent
Food effect	Minimal	Minimal

PK Interaction between NVA237 and QAB149

The PK interaction between glycopyrrolate and indacaterol was investigated in Study QVA149A2107. It was an open-label, randomized, non-confirmatory, 4-period crossover study to assess and compare the systemic exposure of glycopyrrolate and indacaterol after administration of QVA149 27.5/12.5 µg ×2 BID, QAB 27.5 µg ×2 BID, and NVA237 12.5 µg ×2 BID. Results indicated that, following the administration of QVA149, the steady-state systemic exposure (AUC_{0-12h, ss} and C_{max,ss}) to each component was similar as compared to that following each of the monotherapies (Table 3). Therefore, there is no PK interaction between NVA237 and QAB149.

Table 3. Comparison of systemic exposure of indacaterol and glycopyrrolate following the administration of QVA149 or monotherapies

Treatment	Parameter	GMR (90% CI)
QVA149 bid vs. QAB149 bid (FDC) (Mono)	AUC _t	0.95 (0.91, 0.99)
	C _{max}	0.97 (0.93, 1.02)
QVA149 bid vs. NVA237 bid (FDC) (Mono)	AUC _t	1.09 (1.05, 1.13)
	C _{max}	1.07 (0.97, 1.18)

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/s/

LEI HE
02/24/2015

SATJIT S BRAR
02/24/2015