CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207923Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	207923
Submission Date	12/29/2014
Proposed Brand Name	SEEBRI NEOHALER
Generic Name	Glycopyrrolate Inhalation Powder
Clinical Pharmacology Reviewer	Lei He, Ph.D.
Pharmacometrics Reviewer(s)	Lei He, Ph.D. Dinko Rekic, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
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OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Novartis
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	15.6 mcg inhalation powder hard capsule, administered via Neohaler® device
Indication	COPD
Dosage Regimen	15.6 mcg glycopyrrolate (equivalent to12.5 mcg glycopyrronium), BID

1. Executive Summary

Novartis has submitted NDA 207923 seeking the marketing approval for Glycopyrrolate Inhalation Powder (SEEBRI NEOHALER) for "the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema."

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 US

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.

The Sponsor supports this NDA submission with 16 clinical pharmacology studies, of which 5 studies have also been submitted to support NDA 207930 (QVA149, Indacaterol /Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis).

Please note that NVA237 12.5 mcg glycopyrronium is used throughout this review and is equivalent to NVA237 15.6 mcg glycopyrrolate. NVA237 is used to refer to the formulation and dosing. Doses of NVA237 and biofluid concentrations refer to glycopyrronium, the quaternary ammonium ion ('active moiety') of NVA237.

The following are the major findings of the current review:

1) Following oral inhalation of NVA237 via Concept 1 (Neohaler) 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. Cmax of glycopyrronium is reached by 5 minutes following NVA237 inhalation. Renal elimination of parent drug accounts for ~60-70% of systemic clearance, and metabolism and bile excretion account for the non-renal elimination. The apparent elimination half-life of glycopyrronium following oral inhalation administration was ~33 to 53 h. 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 to be low.

2) The dosing regimen and dosing frequency of NVA237 has been adequately explored. Prior to the confirmatory trials, 2 dose ranging trials were conducted in patients with COPD exploring total daily doses from 12.5 mcg to 200 mcg administered once daily (QD) or twice daily (BID). A dose-response relationship was observed for NVA237 12.5 mcg QD, 25 mcg QD, 12.5 mcg BID, 50 mcg QD, 25 mcg BID, 100 mcg QD, and 50 mcg BID. NVA237 12.5 mcg BID dosing regimen 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). Therefore, NVA237 12.5 mcg BID was selected for confirmation in the Phase 3 program.

3) No dosing adjustment is recommended for any intrinsic or extrinsic factors. However, the systemic exposure (AUC last) of glycopyrronium was over 2-fold higher in patients with severe renal impairment (RI) and end stage renal disease (ESRD). The Clinical Pharmacology reviewer recommends inclusion of cautionary labeling language for the use of NVA237 12.5 mcg BID in patients with severe RI and ESRD.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 207923 and finds the application acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

NVA237 is a long-acting muscarinic antagonist (LAMA) 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 NVA237 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 16 clinical pharmacology studies, of which 5 studies have also been submitted to support another NDA 207930 (QVA149, Indacaterol/Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis).

Rationale for Dose and Dosing Frequency Selection

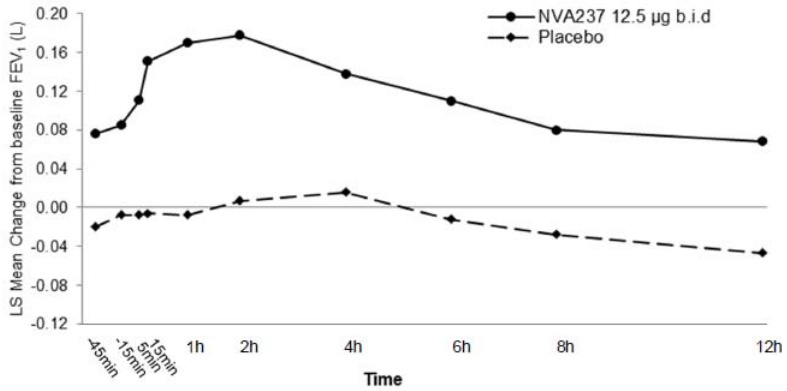
The Clinical Pharmacology reviewer concurs with the selection of NVA237 12.5 mcg BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The dose ranging performed in the NVA237 program was adequate for the Phase 3 dose selection.

The dosing regimen chosen for Phase 3 exploration, including selection of dose and dosing frequency, was established in dose ranging studies with COPD patients. NVA237 12.5 mcg BID dosing regimen 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 2, Figure 1).

Table 2. Mean change from baseline in trough FEV1 for NVA237 (QD vs BID) in StudyNVA237A2208

NVA237 dose	n	LS Mean (SE)	Comparison to Placebo		
		in trough FEV_1 (L)	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)



b.i.d = twice daily; LS mean = least squares mean; FEV_1 = forced expiratory volume in 1 second
Baseline is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1.
Source: [SCE-Appendix 1-Table 2-9.2]

Figure 1 Change from baseline in FEV1 (L) from -45 min to 11 h 55 min on Day 85 (FAS) – pooled analysis of Study NVA237A2317 and A2318
(Source: Figure 4-1, Clinical Overview)

Rationale for Dosing Recommendations in Patients with Renal Impairment

The Clinical Pharmacology reviewer recommends NVA237 12.5 mcg BID for patients with mild and moderate RI. However, for patients with server RI and ESRD, cautionary labeling language should be included.

Following a single NVA237 inhalation 100 mcg, the systemic exposure of glycopyrronium increased with decreasing renal function. Compared to health subjects, the AUClast of glycopyrronium in patients with mild, moderate, server RI and ESRD were 1.42, 1.02, 2.21, and 2.07 fold higher, respectively. Cmax of glycopyrronium were similar or even lower in RI and ESRD patients compared to healthy subjects. The renal clearance of glycopyrronium in subjects with RI was reduced to 62%, 46%, and 20% of that in healthy subjects. Based on these data, the Sponsor recommended no dose adjustments for patients with mild and moderate RI.

Pharmacokinetics

Absorption

- 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.
- Cmax 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.

Distribution

- 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 (Vss) of glycopyrronium was 83 L and the volume of distribution in the terminal phase (Vz) was 376 L. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was 7310 L.

Metabolism and Transporters

- 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.

Elimination

- 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.

COPD vs. Healthy

- There are no clinically relevant differences in systemic exposure to glycopyrronium between healthy subjects and COPD patients.

Population Pharmacokinetic Analysis
Population PK models were developed to describe the NVA237 systemic exposure in COPD patients and to determine if any intrinsic factors influence the systemic exposure.

eGFR and Body Weight
- The identified dependence of apparent total body clearance (CL/F) on age could be explained by a decrease in eGFR with age.
- Systemic exposure to glycopyrronium decreases with increasing patient body weight: Compared to a subject of 74 kg, average exposure was predicted to increase by 47% in a subject of 45 kg, and to decrease by 31% in a subject of 120 kg, respectively.

Considering the limited magnitude of effects, COPD patients can be dosed with NVA237 12.5 mcg BID irrespective of body weight and age.

Gender and Ethnicity
- Gender and ethnicity had no relevant effect on glycopyrronium exposure following NVA237 inhalation.

Special Populations
Renal Impairment
- Following a single NVA237 inhalation 100 mcg, compared to healthy subjects, the AUClast of glycopyrronium in patients with mild, moderate, server RI and ESRD were 1.42, 1.02, 2.21, and 2.07 fold higher, respectively. Cmax of glycopyrronium were similar or even lower in RI patients. No dose adjustments are recommended for subjects with mild and moderate RI. Use with caution in patients with severe RI and ESRD.

Hepatic Impairment
- No clinical studies with NVA237 in patients with hepatic impairment have been conducted.

Drug-Drug Interactions (DDI)

Effect of co-administered drugs on glycopyrronium exposure
- Co-administration of NVA237 with cimetidine (an OCT2 inhibitor) resulted in a modest increase in mean glycopyrronium AUC_{last} by 22% but similar C_{max}. No dose adjustment is recommended when NVA237 is co-administered with cimetidine.
- In NDA207930 submission for QVA149 (Indacaterol/Glycolyrrolate), co-administration of NVA237 with indacaterol did not result in any significant change in glycopyrronium exposure (Cmax,ss and AUCτ,ss), indicating there is no PK interaction between glycopyrrolate and indacaterol.

Effect of glycopyrronium on co-administered drugs exposure
- In NDA207930 submission for QVA149 (Indacaterol/Glycolyrrolate), co-administration of NVA237 did not result in any significant change in indacaterol

exposure (Cmax,ss and AUCτ,ss), indicating there is no PK interaction between glycopyrrolate and indacaterol.

Pharmacokinetic/Pharmacodynamic Relationships for Safety
In the TQT study (Study NVA237A2110), there was no evidence of an exposure-response relationship between systemic exposure (AUClast, Cmax) to glycopyronium at a dose of 400 mcg and the effect of NVA237 on the QTcF as well as on the other cardiac parameters QTcB and heart rate. Overall, all doses administered in Phase I studies in healthy volunteers (HVs) and early patient studies were well tolerated. The frequencies of adverse events and other safety findings were similar for NVA237 12.5 mcg BID and placebo.

2. Question Based Review

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

The submitted *in vitro* studies using human biomaterials are listed in Table 3.

Table 3. In Vitro Studies for NVA237 Using Human Biomaterials

Study/Report name	Objective
DMPK R1200200	Human plasma protein binding
DMPK R0600082	Potential of NVA237 to inhibit CYP450 isoforms
DMPK R0600683	Identify CYP450 isoforms responsible for NVA237 metabolism
DMPK R0800472	Potential of NVA237 to inhibit efflux transporter (MDR1, MXR, MRP2)
DMPK R0800473	Potential of NVA237 to interact with human OCT1 and OCT2 transporters
DMPK R0800502	Potential of NVA237 as an inducer of drug metabolizing enzymes and transporters in human hepatocytes
DMPK R0800758	Uptake transporter (OCT1, OCT2) phenotyping for NVA237
DMPK R0900807	Potential of NVA237 as a substrate of the human multidrug and toxin extrusion transporters, MATE1 and MATE2K
DMPK R1000619	Potential of NVA237 to inhibit CYP2B6
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 R0800705	Potential uptake of NVA237 into human hepatocytes
DMPK R1000635	Assessment of the intestinal transport of NVA237 using the gastrointestinal Caco-2 cell line

The clinical pharmacology studies are summarized in Table 4.

Table 4. Summary of Clinical Pharmacology Studies

	CP Study		Objective	Population	Dosing Regimen	Device
NVA237	1	NVA237A2104	PK, safety	Japanese and Caucasian HS (37)	50, 100, 200 mcg, SD	Concept 1
	2	NVA237A2105	PK in subjects with renal impairment	Renal impairment subjects (30) and HS (18)	100 mcg, SD	Concept 1
	3	NVA237A2107	PK	Chinese HS (12)	50 mcg QD, MD for	Concept 1

					14 days	
	4	NVA237A2108	Absolute BA of NVA237	HS (30)	200 mcg, SD, inhalation, IV, and oral dose	Concept 1
	5	NVA237A2109	Drug interaction with cimetidine	HS (20)	100 mcg, SD	Concept 1
	6	NVA237A2110	Thorough QT study	HS (73)	400 mcg, SD	Concept 1
	7	NVA237A2103	PK, safety, PD	COPD patients (41)	25, 50, 100, 200mcg, QD, MD for 14 days	Concept 1
	8	NVA237A2205	Dose ranging	Japanese and Caucasian COPD patients (83)	12.5, 25, 50, 100 mcg, QD	Concept 1
	9	NVA237A2208	Dose ranging	COPD patients (386)	12.5, 25, 50, 100 mcg, QD for 28 days; 12.5, 25, 50 mcg, BID for 28 days	Concept 1
	10	NVA237A2317	Efficacy, safety, tolerability	COPD patients (441)	12.5 mcg BID	Concept 1
	11	NVA237A2318	Efficacy, safety, tolerability	COPD patients (432)	12.5 mcg BID	Concept 1
QVA149 (QAB149/ NVA237)	12	QVA149A2101	Comparative PK	HS (28)	QVA149 300/100 mcg, SD	Concept 1
	13	QVA149A2103	Comparative PK	HS (43)	QVA149 100/50 mcg QD, MD for 14 days	Concept 1
	14	QVA149A2105	PD (heart rate, serum potassium), safety, PK	HS (50)	QVA149 (440 mcg QAB149/200 mcg NVA237) QAB149 600 mcg	Concept 1 and Diskus (for PC)
	15	QVA149A2106	Comparative PK	HS (24)	QVA149 100/50 mcg QD, MD for 14 days	Concept 1
	16	QVA149A2107	PK interaction between NVA237 and QAB149	HS (36)	QVA149 27.5/12.5 mcg ×2, BID, MD for 14 days	Concept 1

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

Key clinical studies supporting NVA237 12.5 mcg BID dosing regimen are summarized in Table 5.

Table 5. Overview of Clinical Development Program

NVA237	Dose selection study	NVA237A2208	COPD (386), 12.5, 25, 50, 100 mcg, QD for 28 days; 12.5, 25, 50 mcg, BID for 28 days
	Pivotal phase 3 studies	NVA237A2317	COPD (441), 12w, NVA237 12.5mcg BID vs placebo
		NVA237A2318	COPD (432), 12w, NVA237 12.5mcg BID vs placebo
		NVA237A2319	COPD (511), 52w, NVA237 12.5mcg BID vs QAB149 75 mcg QD
QVA149 (QAB149/ NVA237)	Supportive efficacy and safety 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

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

NVA237 (glycopyrronium bromide, described in the Ph. Eur and USP as glycopyrrolate) is a small molecule drug with the molecular structure as shown in Figure 2. Glycopyrronium bromide is a white powder with a molecular formula of $C_{19}H_{28}NO_3$.Br and the molecular weight is 398.33. It has a melting range of 193 – 198°C and is freely soluble in water.

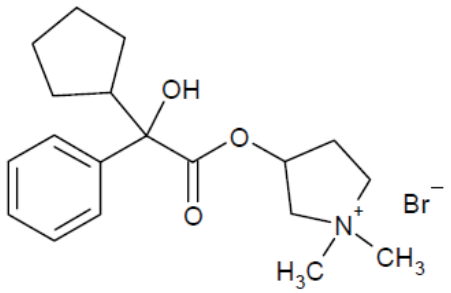


Figure 2. Molecular Structure of Glycopyrrolate

Drug Product

The drug product, NVA237 12.5 mcg inhalation powder, is a white to practically white powder contained in a transparent orange hypromellose capsule, size 3, administered via the Concept1 unit dose dry powder inhaler designed to deliver single dose for oral inhalation. One NVA237 12.5 mcg inhalation powder capsule contains 15.6 mcg of glycopyrronium bromide (glycopyrrolate) corresponding to 12.5 mcg of glycopyrronium base. The composition of drug product is shown in Table 6. NVA237 12.5 mcg inhalation powder capsule is packaged in aluminum/aluminum blisters.

Table 6. Composition of NVA237 12.5 mcg inhalation powder capsule

Ingredient	Amount per capsule (mg)	Function	Reference to standards
Capsule fill			
Glycopyrronium bromide (NVA237)	0.0156[1]	Drug substance	Novartis monograph
Lactose monohydrate	24.9469	(b) (4)	Ph. Eur., USP/NF, Novartis monograph[2]
Magnesium stearate	0.0375		Ph. Eur., USP/NF, Novartis monograph[3]
Capsule fill weight	(b) (4)		
Empty capsule shell, pre-printed			
Capsule shell (theoretical weight)			See Table 2-2
Printing Ink, black			See Table 2-3
Total capsule weight	**74.00**		

1 Corresponds to 0.0125 mg of NVA237 active moiety and a target delivered dose of (b) (4) mcg
2 Novartis monograph contains additional tests as provided in Section [3.2.P.4.1_lactose]
3 Novartis monograph contains additional tests as provided in Section [3.2.P.4.1_mgstearate]

(Source: Table2-1, 3.2.P.1. Description and Composition of the Drug Product)

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

NVA237 is a long-acting muscarinic antagonist (LAMA).

NVA237 is proposed for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

2.2.3 What are the proposed dosages and routes of administration?

NVA237 12.5 mcg inhalation powder capsules are proposed only for oral inhalation and should only be used with the NEOHALER device. The recommended dose is the inhalation of the contents of one 12.5 mcg inhalation powder capsule BID using the NEOHALER device.

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 US can be classified into the following classes:

1. *Bronchodilators*

- β2 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 development program includes full dose-ranging of NVA237 to establish the appropriate dose regimen before proceeding to studies with NVA237 in the Phase 3 program. The selected dosing regimen, 12.5 mcg BID was assessed in Phase 3 program.

Two dose ranging studies were conducted and NVA12.5 mcg BID was selected as the dosing regimen for NVA237.

- 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

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 used trough FEV1 as the primary endpoint in Phase 2 dose ranging/regimen selection studies. The change from baseline in FEV1 $AUC_{0\text{-}12h}$ is the primary endpoints for the primary Phase 3 efficacy studies (NVA237A2317, NVA237A2318)

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

In all relevant studies, only glycopyrronium concentrations were measured. No metabolites were quantified because the metabolites of glycopyrronium 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 NVA237, the systemic exposure is not directly related to clinical response (FEV1). There is evidence of a dose-response relationship with regard to the pertinent pulmonary endpoints. The doses explored in COPD patients included 12.5, 25, 50, 100 mcg QD and 12.5, 25, 50 mcg BID, and a clear dose-response relationship was observed (see section 2.4.2 below).

2.4.2 Has the dosing of NVA237 been adequately explored?

The dosing regimen of NVA237 has been adequately explored in Phase 2 trials.

Two dose ranging trials were conducted in COPD patients:

- Study NVA237A2205 explored NVA237 QD dosing regimen (12.5, 25, 50, and 100 mcg) only, in which the treatment differences (NVA237 vs. placebo) for trough FEV1 on Day 7 were dose-ordered, ranging from 0.075 L (12.5 mcg) to 0.142 L (100 mcg).

- Study NVA237A2208 explored both QD (12.5, 25, 50, and 100 mcg) and BID (12.5, 25, and 50 mcg) dosing regimens. In Study NVA237A2208, 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 7).

Table 7. Mean change from baseline in trough FEV1 for NVA237 (QD vs BID) in Study NVA237A2208

NVA237 dose	n	LS Mean (SE)	Comparison to Placebo		
		in trough FEV_1 (L)	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)

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

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

safety?

In the TQT study (Study NVA237A2110), there was no evidence of an exposure-response relationship between systemic exposure (AUClast, Cmax) to NVA237 at a dose of 400 mcg and the effect of NVA237 on the QTcF as well as on the other cardiac parameters QTcB and heart rate.

Overall, all doses administered in Phase I studies in healthy volunteers (HVs) and early patient studies were well tolerated. The frequencies of adverse events and other safety findings were similar for NVA237 12.5 mcg BID and placebo.

2.4.4 Does this drug prolong QT/QTc Interval?

The effect of NVA237 on the QTcF-interval was evaluated in a randomized, partially-blinded, single dose, placebo and positive (moxifloxacin) controlled three way cross-over study (NVA237A2110), in which healthy subjects received single supra-therapeutic oral inhaled dose of NVA237 400 mcg, placebo, and a single oral dose of moxifloxacin 400 mg. The washout duration between treatment periods was at least 14 days. No clinically relevant effect of NVA237 on the QTcF interval was detected and the mean maximal change from baseline vs. placebo was 2.97 ms (2-sided 90% CI 1.13, 4.80). The upper bound of the 2-sided 90% CI for the mean difference QTcF between NVA237 400 mcg and placebo was less than 5 ms and therefore within the threshold for regulatory concern as described in ICH E14 guideline.

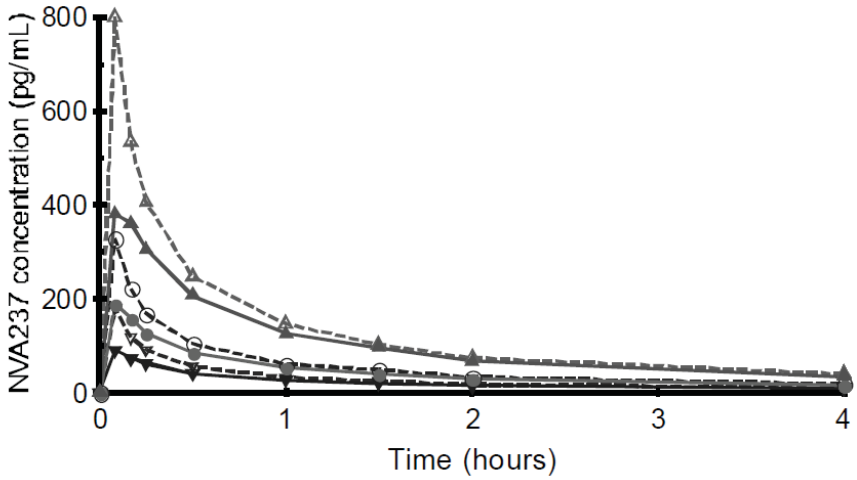
For further details refer to QT/IRT review for NDA207923.

2.5 What are the PK characteristics of the drug?

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 NVA237 was evaluated in Study NVA237A2104. It is a single-center, randomized, double-blind, crossover study, in which 37 healthy male subjects (18 Japanese and 19 Caucasians) received single inhaled doses of NVA237 at 50 mcg, 100 mcg, and 200 mcg using Concept 1 device with a washout period of at least 7 days. The mean plasma concentration-time profile is shown in Figure 3 and the summary of PK parameters is shown in Table 8. Following oral inhalation, Cmax of NVA237 was reached at 5 min (Tmax) at all dose levels. In the dose range of 50 mcg to 200 mcg NVA237, systemic exposure (Cmax and AUC) to glycopyrronium as well as total urinary excretion increased about dose-proportionally after single inhalation in HVs.



Note: for clarity the x axis is shown only up to 4 hours postdose
NVA237 doses in Caucasian (—; closed symbols) and Japanese (---; open symbols) healthy volunteers: ▼ / ▽ = 50 µg; ● / ○ = 100 µg, ▲ / △ 200 µg

Figure 3. Mean plasma NVA237 concentrations vs times following administration of a single dose of NVA237 administered via SDDPI in healthy Caucasian and Japanese subjects
(Source: Figure 11-1, Study NVA237A2104 report)

Table 8. Key plasma and urine PK parameters following single inhaled doses of NVA237 in healthy Caucasian and Japanese subjects

Parameter	Caucasian			Japanese		
	NVA237 50 µg N=19	NVA237 100 µg N=17	NVA237 200 µg N=18	NVA237 50 µg N=17	NVA237 100 µg N=18	NVA237 200 µg N=18
t_{max} [a)] [h]	0.08 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.08)	0.08 (0.02-0.15)	0.08 (0.08-0.17)
C_{max} [pg/mL]	94 (± 35.7)	192 (± 97.2)	401 (± 129)	181 (± 95.6)	328 (± 142)	801 (± 359)
$AUC_{0\text{-tlast}}$ [pg*h/mL]	164 (± 122)	416 (± 181)	968 (± 231)	257 (±154)	578 (± 219)	1269 (± 357)
$AUC_{0\text{-}24}$ [pg*h/mL]	147 (± 77.5)	330 (± 115)	746 (± 175)	209 (±106)	421 (± 147)	930 (± 287)
$Ae_{0\text{-}48}$ [µg]	5.10 (± 2.17)	10.15 (± 3.55)	18.89 (± 6.46)	7.77 (± 2.61)	13.04 (± 4.28)	26.34 (± 6.52)
$Ae_{0\text{-}48}$ [% dose]	10.2 (± 4.34)	10.2 (± 3.55)	9.45 (± 3.23)	15.5 (± 5.23)	13.0 (± 4.28)	13.2 (± 3.26)
CL_R [L/hr]	n.d.	24.4 (± 5.00)	19.8 (± 5.38)	n.d.	23.5 (± 4.89)	21.4 (± 4.47)

n.d.= not determined; [a)] median (min-max)
(Source: Table 11-3, Study NVA237A2104 report)

Multiple dose PK

Multiple dose PK of NVA237 was characterized in Chinese HVs in Study NVA237A2107. The mean plasma PK profiles are shown in Figure 4 and summary PK parameters are listed in Table 9 and 10. The steady state of NVA237 was achieved after 5 days of daily dosing. The mean effective half-life (T1/2, acc) determined based on the accumulation ratio was 37.7 h.

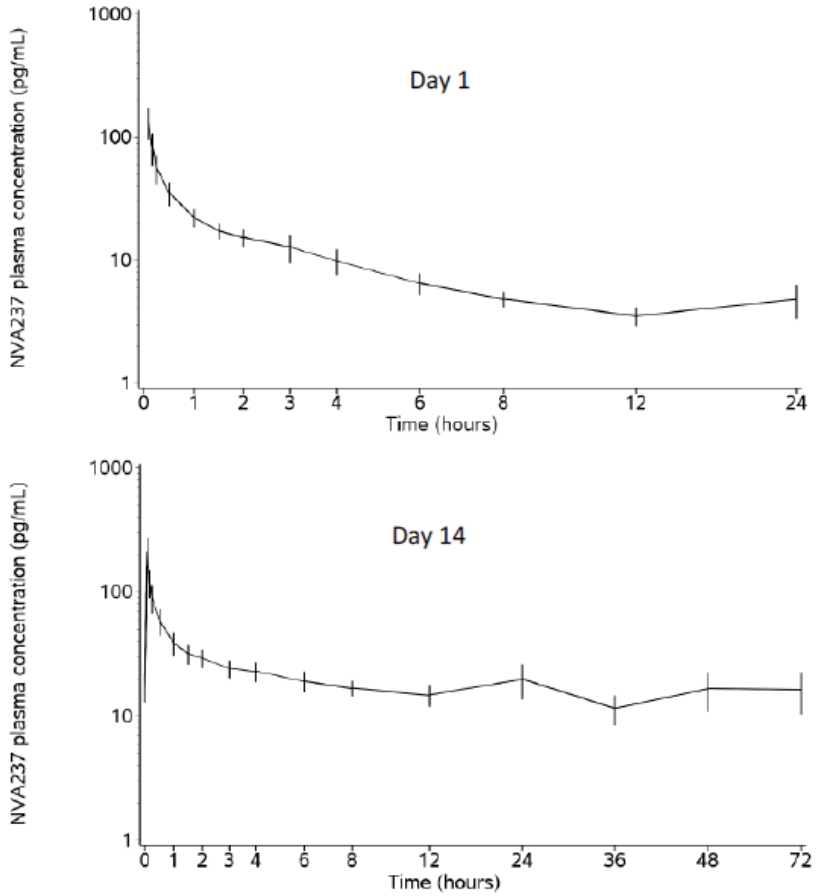


Figure 4. Mean plasma NVA237 concentrations vs time profiles on Day 1 and Day 14 following 14-day NVA237 50 mcg QD administration using Concept 1 in healthy subjects
(Source: Figure 11-1, Study NVA237A2107 report)

Table 9. PK parameters of NVA237 on Day 1 following 14-day NVA237 50 mcg QD administration using Concept 1 in healthy volunteers

PK parameter (unit)	NVA237 50 µg Mean ± SD (% CV) [n]
AUC0-24h (hr*pg/mL)	185 ± 26.2 (14.2) [12]
Cmax (pg/mL)	134 ± 38.3 (28.7) [12]
Tmax (hour)**	0.08 (0.08-0.12) [12]

(Source: Table 11-3, Study NVA237A2107 report)

Table 10. PK parameters of NVA237 on Day 14 following 14-day NVA237 50 mcg QD administration using Concept 1 in healthy volunteers

PK parameter (unit)	NVA237 50 µg Mean ± SD (% CV) [n]
Cmax,ss (pg/mL)	213 ± 57.1 (26.8) [12]
AUC0-24h,ss (hr*pg/mL)	511 ± 65.6 (12.8) [12]
Tmax (hr)**	0.08 (0.08-0.08) [12]
Cmin,ss (pg/mL)	13.5 ± 1.65 (12.2) [12]
Cav,ss (pg/mL)	21.3 ± 2.73 (12.8) [12]
T1/2,acc (hr)	37.7 ± 7.53 (20.0) [12]
Racc	2.80 ± 0.445 (15.9) [12]
Fluc (%)	931 ± 213 (22.9) [12]

(Source: Table 11-4, Study NVA237A2107 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 systemic exposure to glycopyrronium between healthy subjects and COPD patients after single dose and at steady state following BID or QD administration (Table 11 and 12).

Table 11. Summary of glycopyrronium PK parameters [mean (SD)] after a single dose of NVA237 in COPD patients and healthy volunteers

Study	Specifics	Dose [µg] (N)	Cmax [pg/mL]	Tmax [h] [a]	AUC0-24h [pg*h/mL]	AUClast [pg*h/mL]	AUCinf [pg*h/mL]	T1/2 [h]	Ae0-t [b] [% dose]	CLr [L/hr]
NVA237A2103	COPD patients	25 (8)	41 (20.8)	0.08 (0.08-0.25)	n.d.	-	-	n.d	6.68 (2.40) [c]	n.d
		50 (7)	146 (109)	0.08 (0.08-0.50)	n.d.	-	-	n.d	7.74 (2.90)	n.d
		100 (8)	360 (79.6)	0.08 (0.08-0.12)	568 (146)	-	-	13.7 (2.46) [c]	9.80 (2.52) [c]	17.4 (4.62) [c]
		200 (9)	565 (248)	0.08 (0.07-0.50)	1028 (320)	-	-	13.0 (9.30) [c]	9.81 (2.19) [d]	20.6 (3.88) [d]
NVA237A2104	Caucasian HV	50 (19)	94 (35.7)	0.08 (0.08-0.25)	147 (77.5)	164 (122)	-	-	10.2 (4.34)	n.d.
		100 (17)	192 (97.2)	0.08 (0.08-0.25)	330 (115)	416 (181)	-	-	10.2 (3.55)	24.4 (5.00)
		200 (18)	401 (129)	0.08 (0.08-0.25)	746 (175)	968 (231)	-	-	9.45 (3.23)	19.8 (5.38)
	Japanese HV	50 (17)	181 (95.6)	0.08 (0.08-0.08)	209 (106)	257 (154)	-	-	15.5 (5.23)	n.d.
		100 (18)	328 (142)	0.08 (0.02-0.15)	421 (147)	578 (219)	-	-	13.0 (4.28)	23.5 (4.89)
		200 (18)	801 (359)	0.08 (0.08-0.17)	930 (287)	1269 (357)	-	-	13.2 (3.26)	21.4 (4.47)
NVA237A2105	HV only	100 (18)	356 (164)	0.08 (0.08-0.17)	-	821 (288)	1020 (400) [e]	32.5 (23.4) [e]	20.0 (6.38)	23.0 (7.50)
NVA237A2107	Chinese HV	50 (12)	134 (38.3)	0.08 (0.08-0.12)	185 (26.2)	-	-	n.d	-	-
NVA237A2108	ih w/o c in HV	200 (18)	858 (391)	0.08 (0.07-0.17)	968 (173)	1541 (259)	2090 (462) [e]	52.5 (12.7) [e]	15.2 (4.13)	23.1 (7.46)
NVA237A2109	NVA237 alone in HV	100 (20)	323 (149)	0.08 (0.07-0.13)	434 (133)	771 (251)	1000 (421) [c]	45.3 (22.2) [c]	16.4 (4.31) [f]	21.2 (4.14) [f]
NVA237A2110	NVA237 alone in HV	400 (70)	1495 (748)	0.12 (0.05-0.28)	-	1964 (598)	-	-	-	-
QVA149A2101	NVA237 alone in HV	100 (28)	249 (121)	0.08 (0.08-1.00)	409 (104)	532 (171)	-	33.4 (22.9) [g]	-	-
QVA149A2105	NVA237 alone in HV	200 [h] (29)	321 (90.2)	3.08 (1.08, 3.12)	970 (200)	1020 (209)	o.d.	-	-	-

[a] median (range), [b] Ae0-24h in Study NVA237A2103, Ae0-48h in Study NVA237A2104, Ae0-72h in studies NVA237A2108 and NVA237A2109, Ae0-96h in Study NVA237A2105
[c] N=7, [d] N=8, [e] N=12, [f] N=18, [g] N=9, [h] Doses were administered by oral inhalation in a cumulative fashion in four steps separated by 60 minutes 50 µg x 4 steps), n.d. = not determined, - = not calculated, ih w/o c = inhaled with/without charcoal, HV = human volunteer:

(Source: Table 5-1, Summary of Clinical Pharmacology)

Table 12. Summary of glycopyrronium PK parameters [mean (SD)] at steady state after NVA237 inhalation in COPD patients and healthy volunteers

Study	Specifics Dosing regimen (o.d./b.i.d.)	Dose [µg] (N)	Cmax, ss [pg/mL]	Tmax, ss [h] [a]	AUCtau,ss [pg*h/mL] [b]	T1/2 [h]	Aetau [% dose] [b]	CLr [L/hr]
NVA237A2103	COPD patients	25 (8)	51 (17.4)	0.11 (0.08-0.25)	n.d.	n.d	11.6 (4.42)	n.d
	o.d.	50 (8)	166 (97.3)	0.08 (0.08-0.25)	464 (213)	13.4 (8.02) [c]	14.4 (3.36)	17.6 (6.40)
		100 (8)	436 (135)	0.08 (0.08-0.25)	778 (155)	20.8 (8.61) [d]	14.1 (5.04)	18.6 (6.20)
		200 (8)	865 (545)	0.08 (0.08-0.10)	1780 (653)	21.6 (3.24) [c]	15.0 (5.38)	17.4 (4.57)
NVA237A2107	Chinese HV o.d.	50 (12)	213 (57.1)	0.08 (0.08-0.08)	511 (65.6)	n.d.	-	-
QVA149A2103	NVA237 only in HVs o.d	50 (39)	117 (57.3)	0.08 (0.08-0.25)	396 (144)	-		-
QVA149A2106	NVA237 only in HVs o.d	50 (24)	216 (148)	0.08 (0.08-0.18)	558 (228)	-		-
QVA149A2107	NVA237 12.5 µg b.i.d. x2 only in HV	25 [e] (32)	71.9 (31.1)	0.08 (0.08-0.25)	221 (50.6)	-		-

[a] median (range), [b] tau is the dosing interval and equals to 24 hours for the o.d. treatments and 12 hours for the b.i.d. treatments, [c] N=4, [d] N=3, [e] Dose given as 2 x 12.5 µg, n.d=not determined, - = not calculated in this study, HV = healthy volunteer

(Source: Table 5-2, Summary of Clinical Pharmacology)

2.5.3 What are the characteristics of drug absorption?

Following oral inhalation of NVA237 via Concept 1 device, glycopyrronium was absorbed rapidly with Tmax of 5 min post dose. Compared to intravenous (mean T1/2: 6.2 h) and oral (mean T1/2: 2.8 h) administration, the terminal elimination phase was much longer after inhalation (mean T1/2: 33 to 53 h), indicating a sustained lung absorption and/or transfer of NVA237 into the systemic circulation. The estimate of absolute bioavailability for NVA237 inhalation via Concept 1 device was ~40% (Table 13). About 90% of systemic exposure is due to lung absorption and 10% is due to gastrointestinal absorption (Table 14).

Table 13. Summary of the analysis of absolute bioavailability (Fabs)

Parameter	Comparison	Fabs in % (90% CI)
AUClast (h*pg/mL)	inh. NVA237 200 µg without charcoal to i.v. glycopyrrolate 120 µg	32.0 (30.1, 34.1)
AUCinf (h*pg/mL)	inh. NVA237 200 µg without charcoal to i.v. glycopyrrolate 120 µg	42.3 (38.3, 46.6)

inh. = inhaled. Source: PT-Table 14.2-1.2.1

(Source: Table 11-6, Study NVA237A2108 report)

Table 14. Summary of the analysis of relative bioavailability (Flung)

Parameter	Comparsion	Flung in % (90% CI)
AUClast (h*pg/mL)	inh. NVA237 200 µg with charcoal to inh. without charcoal	86.4 (80.6, 92.6)
Cmax (pg/mL)	inh. NVA237 200 µg with charcoal to inh. without charcoal	85.0 (74.6, 96.8)
AUCinf (h*pg/mL)	inh. NVA237 200 µg with charcoal to inh. without charcoal	97.1 (89.7, 105)

inh = inhaled. Source: PT-Table 14.2-1.3.1

(Source: Table 11-7, Study NVA237A2108 report)

2.5.4 What are the characteristics of drug distribution?

Following intravenous dosing, the average steady-state volume of distribution (V_{ss}) of glycopyrronium was estimated to be 83 L and the volume of distribution in terminal phase (Vz) was estimated to be 376 L, suggesting distribution into tissues. The apparent volume of distribution in the terminal phase following inhalation (Vz/F) was estimated to be 7310 L. In vitro studies determined the plasma protein binding of glycopyrronium was 38% to 41% at concentrations of 1 to 10 ng/mL.

2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study has been conducted in this application. After IV administration, about 61% of systemic clearance of NVA237 is accounted for by the renal elimination of the drug, while 39% of systemic clearance is due to non-renal mechanisms (Study NVA237A2108). Following inhalation of single and repeated once-daily doses between 50 and 200 mcg NVA237, about 7.7% -20.0% of the administered glycopyrronium excreted into the urine. Population PK analysis indicated that the estimates for the renal and non-renal contributions to total clearance are 69% and 31%, respectively.

Overall, the renal elimination of parent drug accounts for about 60 to 70% of the systemic clearance of glycopyrronium whereas non-renal clearance processes account for about 30% to 40%, both after intravenous administration and inhalation.

It has been reported that biliary clearance (about 5% after IV dosing) contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism (oxidation, glucuronidation/sulfation and hydrolysis).

2.5.6 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

No mass balance study has been conducted using radiolabelled glycopyrronium in this application.

After IV administration, on average, 60.6% of the intravenous dose was recovered from the urine as parent drug (Study NVA237A2108). Glucuronide and/or sulfate conjugates of glycopyrronium were found in urine of humans after repeated inhalation, accounting for about 3% of the dose (Study NVA237A2103).

It has been reported in the literature that in humans, after IV administration of [^{3}H]glycopyrrolate (0.003 mg/kg), the mean urinary excretion in 48h amounted to 85% of the total amount of radioactivity. At least 80% of the radioactivity in urine was attributed to parent drug and the rest was attributed to metabolites, but these were not further characterized. Small amounts of radioactivity (~5%) were also found in bile, with similar parent to metabolite ratios as in urine.

2.5.7 What are the characteristics of drug metabolism?

The *in vitro* metabolism of glycopyrrolate in human liver microsomes and hepatocytes was slow (Figure 5). Besides hydroxylation and oxidation, glycopyrronium was hydrolyzed to the

minor cleavage product M9, which is an inactive metabolite. And no glucuronides or glutathione (GSH) adducts could be observed.

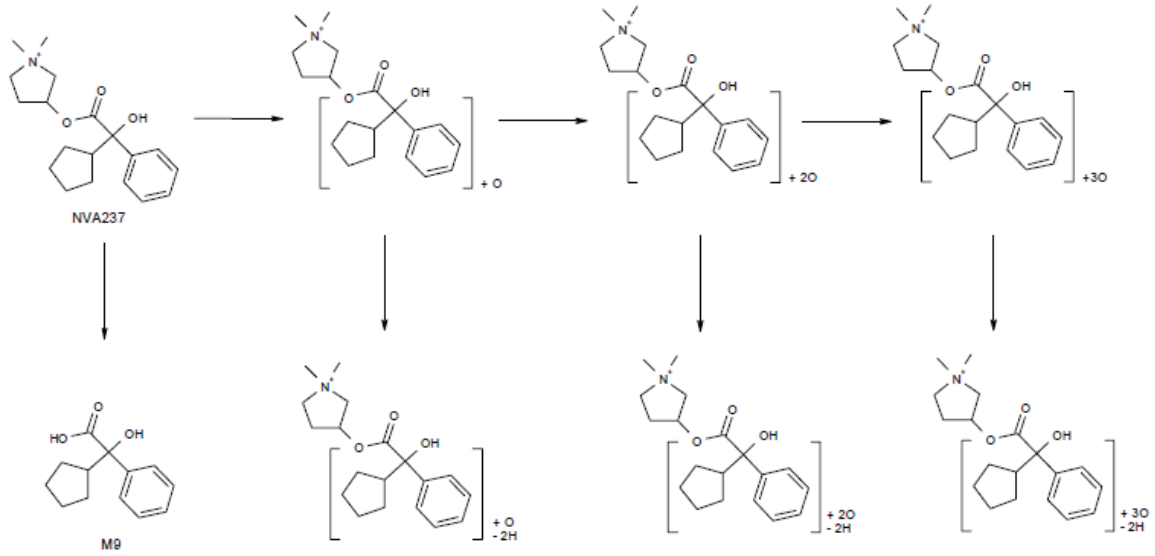


Figure 5. Main in vitro biotransformation pathways of glycopyrrolate
(Source: Figure5-3, Summary of Clinical Pharmacology)

The proposed *in vivo* metabolic pathways for NVA237 are shown in Figure 6. Both in vitro and in vivo studies indicate that glycopyrrolate undergoes biotransformation by three primary pathways:

i. addition of 1, 2 or 3 oxygen atoms to the cyclopentyl and phenyl ring moieties forming metabolites M1, M3, M5, M6, M7, M10, M15, M18, M23, M29 or M35
ii. subsequent dehydrogenation on the cyclopentyl ring forming M2, M8, M11, M12, M13, M14, M16, M17 or M19, and
iii. hydrolysis of the ester linkage to form the corresponding carboxylic acid metabolite M9.

After inhalation of NVA237, systemic exposure to M9 was on average in the same order of magnitude as the exposure to the parent drug. However, when the gastrointestinal absorption is blocked (i.e. with oral activated charcoal), M9 was not present in plasma after NVA237 inhalation, indicating M9 is formed from the swallowed dose fraction of orally inhaled glycopyrrolate by pre-systemic hydrolysis.

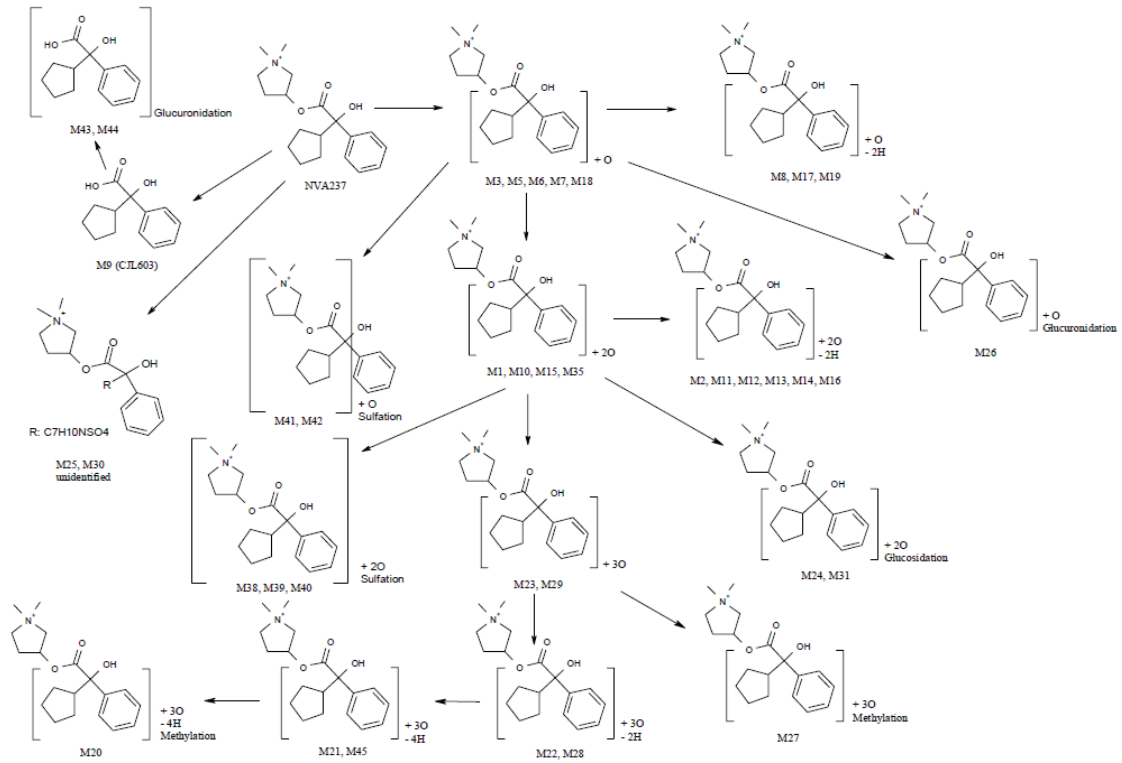


Figure 6. Main in vivo metabolic pathways of glycopyrrolate in mammals
(Source: Figure 10-3, Pharmacokinetic written summary)

2.5.8 Is there evidence for excretion of parent drug and/or metabolites into bile?

There is no evidence for biliary excretion from studies in this application.

It has been reported in the literature that biliary excretion accounts for 5% of glycopyrrolate clearance after IV administration.

2.5.9 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

The available plasma concentration-time profile information does not suggest enterohepatic recirculation for glycopyrrolate.

2.5.10 What are the characteristics of drug excretion in urine?

Parent drug was the major drug-related component in urine, accounting for about 60 to 70% of the systemic clearance of glycopyrronium after IV or inhalation administration. Following inhalation of single and repeated once-daily doses between 50 and 200 mcg NVA237 by HVs and patients with COPD, the mean amounts of glycopyrronium excreted into the urine are between 7.7% and 20.0% of the dose, depending on the time interval considered (up to 24, 48, 72 or 96h). Glucuronide/sulfate conjugates accounted for about 3% of the dose at steady state, and the hydrolysis metabolite M9 accounted for about 0.5% of the dose after a single inhalation.

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

Population PK analysis indicated that following inhalation of NVA237 from 12.5 mcg

BID to 50 mcg QD, the PK of glycopyrronium are linear in COPD patients.

In Study NVA237A2104 in healthy Caucasian and Japanese volunteers, following a single NVA237 inhalation at doses of 50, 100, and 200 mcg, Cmax was shown to increase dose-proportionally over dose range of 50 to 200 mcg in both ethnic groups. AUC0-24h was considered more than dose-proportional to the increase in dose (Table 15).

Table 15. Estimate of the slope for a linear regression between log-PK parameter and log-dose in Study NVA237A2104

Ethnic Group	PK Parameter	Effect	Point Estimate	90% CI
Caucasian	Cmax	Log (dose)	1.07	(0.96, 1.19)
	AUC0-24	Log (dose)	1.22	(1.12, 1.33)
Japanese	Cmax	Log (dose)	1.10	(0.99, 1.22)
	AUC0-24	Log (dose)	1.16	(1.05, 1.27)

* The critical region for the 90% confidence interval of the slope in order to conclude dose-proportionality across the entire dose range is (0.74, 1.26).
**AUC0-24, no AUCinf
(Source: adapted form Table 3-1, Summary of Clinical Pharmacology)

In Study NVA237A2103 in COPD patients, following repeated NVA237 once-daily inhalation, systemic exposure (Cmax, AUC0-24h) were shown to increase about dose-proportionally over the 50 to 200 mcg range.

Table 16. Summary of glycopyrronium PK parameters [mean(SD)] after single and multiple NVA237 QD inhalation in COPD patients in Study NVA237A2103

PK Parameter (Day 1) [mean (SD)]	**25 mcg (N=8)**	**50 mcg (N=7)**	**100 mcg (N=8)**	**200 mcg (N=8)**
Tmax (h)*	0.08 (0.08-0.25)	0.08 (0.08-0.50)	0.08 (0.08-0.12)	0.08 (0.07-0.50)
Cmax (pg/mL)	41 (20.8)	146 (109)	360 (79.6)	565 (248)
AUC0-24h (pg*h/mL)	NA	NA	568 (146)	1028 (320)
T1/2 (h)	NA	NA	13.7 (2.46)	13.0 (9.30)
CLr (L/h)	NA	NA	17.4 (4.62)	20.6 (3.88)
PK Parameter (Day 14) [mean (SD)]	**25 mcg (N=8)**	**50 mcg (N=8)**	**100 mcg (N=8)**	**200 mcg (N=8)**
Tmax (h)	0.11 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.10)
Cmax (pg/mL)	51 (17.4)	166 (97.3)	436 (135)	865 (545)
AUC0-24h (pg*h/mL)	NA	464 (213)	778 (155)	1780 (653)
T1/2 (h)	NA	13.4 (8.02)	20.8 (8.61)	21.6 (3.24)
CLr (L/h)	NA	17.6 (6.4)	18.6 (6.20)	17.4 (4.57)

*Median (range)
(Source: adapted form Table 11-3, Study NVA237A2103)

It should be noted that due to the low concentrations and a relatively limited assay sensitivity (LLOQ of 4 pg/mL) of the analytical method used for Study NVA237A2103 and A2104, AUC0-24h and T1/2 values are not available for all subjects with 25 and 50 mcg dose.

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

In Study NVA237A2103 in COPD patients, following repeated NVA237 once-daily inhalation, Tmax and renal clearance of glycopyrronium were similar after single and repeated dosing, suggesting a time-independent PK following once-daily inhaled administration (Section 2.5.11, Table16).

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

The circadian rhythm of NVA237 PK was not evaluated in this NDA.

2.6 Intrinsic Factors

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 glycopyrronium systemic exposure in patients with COPD. Please see Pharmacometrics Review in Appendix 4.1 for additional details.

Body weight and eGFR was identified as intrinsic factors contributing to the inter-subject variability in glycopyrronium systemic exposure in COPD patients. The systemic exposure of glycopyrronium decreases with the increase of body weight. Compared to subjects of 74kg, the average exposure of glycopyrronium was predicted to increase by 47% and decrease by 31% in subjects of 45 kg and 120 kg, respectively. The contribution of eGFR on glycopyrronium systemic exposure can also explain the apparent dependence of CL/F on age because eGFR decreases with age. However, with the limited magnitude of effect, no dose adjustments are recommended.

There is no effect of gender, smoking status, baseline FEV1, and ethnicity on the systemic exposure of glycopyrronium in COPD patients.

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 NVA237 is indicated for the treatment of adult COPD patients only. Pharmacokinetic studies with inhaled NVA237 were not conducted in children (<18 years old).

2.6.2.5 Race/Ethnicity

As stated in section 2.6.1.

Population PK
In population PK analysis including 38 Hispanic/Latino patients and 27 Japanese patients, the AUC values were similar between the populations at the same dose level. However, the Cmax was 19% higher in Japanese patients compared with other ethnicities.

Single dose PK in Chinese, Japanese, and Caucasian
A cross-study comparison of glycopyrronium PK among healthy Chinese subjects (Study NVA237A2107), Caucasian COPD patients (Study NVA237A2103), and healthy Caucasian and Japanese subjects (Study NVA237A2104) indicated that after a single 50 mcg dose of NVA237 inhalation via Concept 1, there is no clinically relevant difference in systemic exposure of glycopyrronium across the studied ethnic groups (Figure 7).

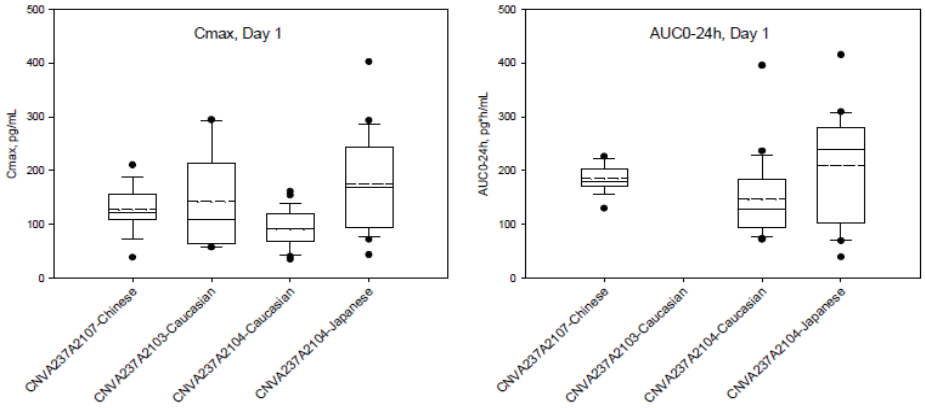


Figure 7. Comparison of Cmax and AUC0-24h of glycopyrrolate across different ethnic groups following single 50mcg dose of NVA237 inhalation via Concept 1
Note: Solid lines are median, dashed lines are mean, boxes depict 25th~75th percentile, Whiskers above and below the box indicate the 90th and 10th percentiles.
AUC0-24h, Day 1 is unavailable in NVA237A2103.
(Source: Figure 3-6. Summary of Clinical Pharmacology)

Multiple dose PK at steady state in Chinese and Caucasian
A cross-study comparison of the systemic exposure (Cmax,ss and AUC0-24h,ss) of glycopyrronium at steady state among Chinese HVs (Study NVA237A2107), Caucasian COPD patients (Study NVA237A2103), and Caucasian HVs (Study QVA129A2106) indicated that after once daily 50 mcg dose of NVA237 inhalation via Concept 1 for 14

days, there is no clinically relevant difference in systemic exposure of glycopyrronium at steady state across the studied ethnic groups (Figure 8).

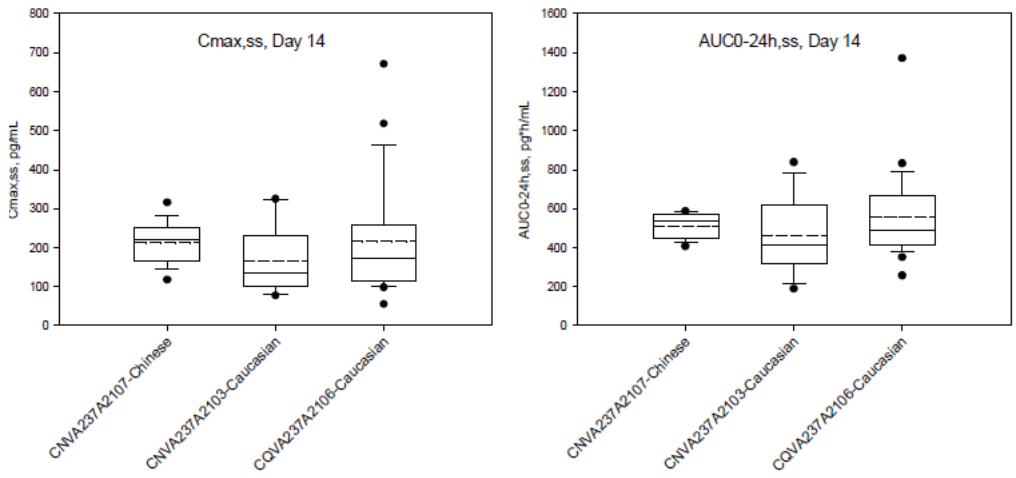


Figure 8. Comparison of Cmax,ss and AUC0-24h,ss of glycopyrronium at steady state across different ethnic groups following multiple QD inhalation of NVA237 50mcg via Concept 1 for 14 days

Note: Solid lines are median, dashed lines are mean, boxes depict 25th~75th percentile, Whiskers above and below the box indicate the 90th and 10th percentiles.
(Source: Figure 3-7. Summary of Clinical Pharmacology)

2.6.2.6 Renal Impairment

Renal excretion of unchanged NVA237 is the major elimination pathway of systemically available drug, accounting for 60% to 70% of the total clearance. The impact of renal function on glycopyrronium PK was evaluated in subjects with various degrees of RI and healthy controls in Study NVA237A2105 (Figure 9 and Table 17). Following a single NVA237 inhalation (100 mcg), the systemic exposure of glycopyrronium increased with decreasing renal function. Compared to HVs, the AUClast of glycopyrronium in patients with mild, moderate, server RI and ESRD were 1.42, 1.02, 2.21, and 2.07 fold higher, respectively. Cmax of glycopyrronium were similar or even lower in RI patients compared to HVs. The renal clearance of glycopyrronium in subjects with RI reduced to be 62%, 46%, and 20% of that in HVs.

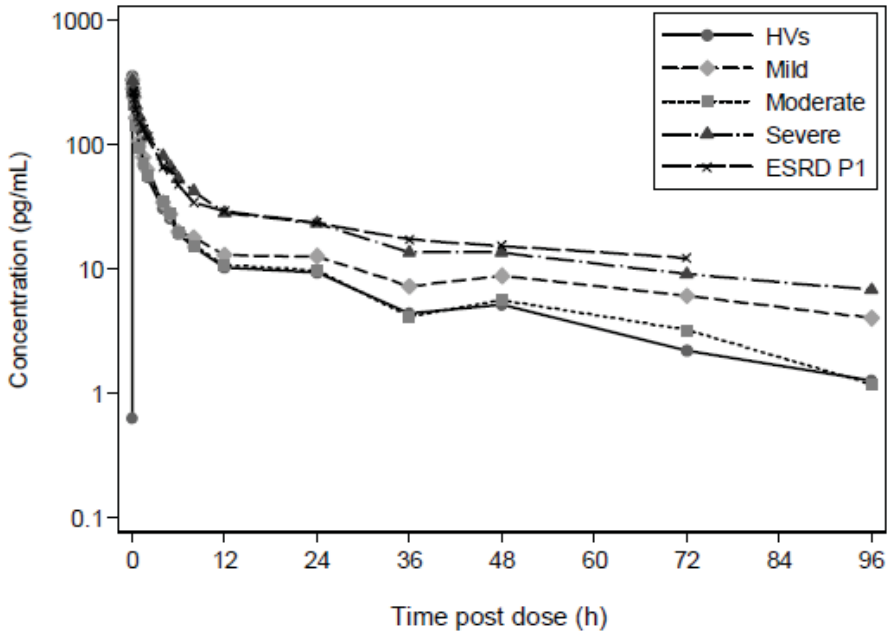


Figure 9. Mean plasma concentration time-profiles of glycopyrronium in subjects with various degrees of renal impairment and healthy subjects following a single inhalation of 100 mcg NVA237

ESRD P1: end-stage-renal-disease subjects requiring dialysis and NVA237 was administered between two dialysis sessions (period 1)

(Source: Figure 11-1, Study NVA237A2105 report)

Table 17. Summary of primary PK parameters of glycopyrronium in subjects with various degrees of renal impairment and healthy subjects following a single inhalation of 100 mcg NVA237

Parameter	RI group	Ratio vs HV (90% CI) Sensitivity analysis
AUClast	Mild	1.42 (1.08, 1.87)
(hr*pg/mL)	Moderate	1.02 (0.78, 1.35)
	Severe	2.21 (1.45, 3.36)
	ESRD	2.07 (1.35, 3,19)
Cmax	Mild	0.94 (0.68, 1.30)
(pg/ml)	Moderate	0.76 (0.53, 1.10)
	Severe	0.98 (0.76, 1.27)
	ESRD	0.83 (0.56, 1.23)
CLr (L/hr)	Mild	0.62 (0.49, 0.79)
	Moderate	0.46 (0.37, 0.58)
	Severe	0.20 (0.14, 0.28)

(Source: Table 11-6, Study NVA237A2105 report)

2.6.2.7 Hepatic Impairment

~30-40% of total systemically available glycopyrronium are cleared by metabolism/bile excretion. No dedicated study was conducted in hepatic impairment patients in this NDA as majority of the elimination is via renal route of unchanged drug.

2.6.3 Does genetic variation impact exposure and/or response?

The pharmacogenetic impact was not assessed.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Glycopyrrolate does not significantly inhibit or induce CYP enzymes, ATP-binding cassette (ABC) transporters, and solute carrier (SLC) transporters at therapeutic concentrations, suggesting the potential for relevant drug-drug interaction appears to be low.

Glycopyrrolate is a substrate of the cationic SLC transporter OCT2 (organic cation transporter 2) and MATE1 (multidrug and toxin extrusion protein), which are likely involved in the renal tubular secretion of glycopyrrolate in humans. Inhibition of either OCT2 or MATE1 may affect glycopyrrolate renal excretion and PK.

Please see sections 2.7.2 and 2.7.4 for further details.

2.7.2 Is the drug a substrate of CYP enzymes?

In vitro studies suggest multiple CYP isoenzymes, including CYP2D6, CYP1A2, CYP2B6, CYP2C9, CYP2C18, CYP2C19 and CYP3A4 catalyze the biotransformation of glycopyrrolate, of which CYP2D6 contributed predominantly. The involvement of multiple CYP isoenzymes suggests that the metabolism of NVA237 may not be readily inhibited by a single specific CYP inhibitor. In addition, the relative contribution of metabolism to total clearance of systemically available glycopyrronium after inhalation is estimated with maximal 30 to 40% in human. Therefore, drug-drug interactions due to inhibition or induction of NVA237 metabolism by co-medications are expected to be of minor clinical importance.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes/transporters?

Glycopyrrolate 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.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

Glycopyrrolate is a substrate for the cationic SLC transporter OCT2 and MATE1, which are likely involved in the renal tubular secretion of glycopyrrolate in humans. Inhibition of OCT2 or MATE1 may affect glycopyrrolate renal excretion and PK.

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transporters are known to be important for disposition of glycopyrrolate in addition to those already discussed in sections 2.7.2 and 2.7.4

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

With regard to extrinsic factors, only the effect of co-administration with other drugs on NVA237 exposure has been evaluated, which is discussed under section 2.7.7. The differences in measured systemic exposures are not relevant for efficacy.

2.7.7 What are the drug-drug interactions?

The drug interaction between NVA237 and cimetidine, an OCT2 inhibitor, was assessed in HVs in Study NVA237A2109. The effect of co-administered cimetidine on NVA237 PK is summarized in Table 18. According to the magnitude of the PK changes (22% increase in AUClast and similar Cmax) of NVA237, the effect of co-administered cimetidine on NVA237 is clinical irrelevant.

Table 18. Effect of co-administered drugs on NVA237

Co-administered drug	**Co-administered drug**	**GMR* (90% CI)**	
		AUClast	**C_{max}**
Cimetidine (OCT2 inhibitor) 800 mg BID (monotherapy on days 1-6, with NVA237 on day 4)	NVA237 (100 mcg) single inhalation on the 4th day of a 6-day treatment period with cimetidine	1.22 (1.12-1.32)	0.94 (0.82-1.07)

*GMR: Ratio of Geometric Means
(Adapted from Table 11-4, Study NVA237A2109 report)

In NDA207930 submission for QVA149 (fixed-dose combination of glycolyrrolate 27.5 mcg/indacaterol 12.5 mcg, Concept 1 device) submitted by Novartis on 12/29/2014, the PK interaction between glycopyrrolate 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 (AUC0-12h,ss; Cmax,ss) to indacaterol and glycopyrronium was similar between the combination product and monotherapies (Table 19).

Table 19. Comparison of glycopyrrolate and indacaterol PK parameters following BID administration of QVA149 and each drug inhaled alone

Compound	Parameter	GMR (90% CI)
Glycopyrrolate	Cmax,ss	1.07 (0.97, 1.18)
	AUC0-12h,ss	1.09 (1.05, 1.13)
Indacaterol	Cmax,ss	0.97 (0.93, 1.02)
	AUC0-12h,ss	0.95 (0.91, 0.99)

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

The PK information from the drug interaction studies which were conducted at higher doses can be extrapolated to the proposed dose, 12.5 mcg BID NVA237.

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

The NVA237 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?

Glycopyrolate is a LAMA. Co-administration of anticholinergics may lead to an increase in anticholinergic 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?

This is an inhalation drug and the sponsor did not provide BCS classification information 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 NVA237 12.5 mcg inhalation powder hard capsule administered via the Concept1 unit dose dry powder inhaler. It was used in key studies of the clinical development program, including the dose selection study (Study NVA237A2208) and pivotal phase 3 studies (Studies NVA237A2317, A2318, and A2319).

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 NVA237 is not assessed. Since the oral bioavailability of NVA237 is minimal, it is not likely that inhaled NVA237 PK is changed by food.

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, NVA237 12.5 mcg, was proposed for the to-be-marketed product. Dose strengths of NVA237 of 12.5, 25, 50, 100, and 200 mcg for inhalation with the Concept1 device have been used in biopharmaceutical and clinical PK studies. (b) (4) [redacted]. No studies were conducted to test the bioequivalence of the different strength.

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

All the validation reports of analytical methods which were used for the determination of different analyte in human plasma, urine and dialysate submitted in this NDA are summarized in Table 20.

Three analytical methods were used for glycopyrromium measurement in human plasma, of which the method R0900330C (with amendment R0900330C 01) was improved to a LLOQ of 1.5 pg/mL for glycopyrromium and was used in NVA12.5 mcg clinical development. The LLOQs of methods R0900330 and R0600354 are 3.0 and 4.0 pg/mL, respectively, and both methods were used in relevant clinical pharmacology studies. The validation reports of the three analytical methods for glycopyrromium measurement in human plasma are summarized in Table 21.

The analytical methods for the determination of glycopyrromium in urine, M9 (inactive metabolite) in plasma and urine were also validated but not be summarized in this review.

Table 20. Validation reports of analytical methods used in NVA237 clinical trials

Analyte	**Matrix**	**Validation Report**	**Clinical studies supported**
Glycopyrronium	Plasma	**R0600354A-01, R0600354A-02**	NVA237A2103 NVA237A2104 QVA149A2101
		R0900330, R0900330-02	NVA237A2105 NVA237A2108 NVA237A2109 NVA237A2110 NVA237A2303 NVA237A2304 QVA149A2103 QVA149A2105 QVA149A2106
		R0900330C, R0900330C-01	NVA237A2107 NVA237A2317 NVA237A2318 QVA149A2107
Glycopyrronium	Urine	R0600354E	NVA237A2103 NVA237A2104
		R0900330A	NVA237A2105 NVA237A2108 NVA237A2109
Glycopyrronium	Dialysate	R0900330B	NVA237A2105
QBA608 and QBA609*	Urine	R0600354B, R0600354B-01	NVA237A2103 NVA237A2104
Glycopyrronium (total)**	Urine	R0600354G	NVA237A2103
M9	Plasma	R1100006, R1100006-01	NVA237A2108
M9	Urine	R1100006C, R1100006C-01	NVA237A2108

* QBA608 and QBA609 are enantiomers of glycopyrronium

**Total glycopyrronium = sum of parent glycopyrronium + glucuronide/sulfate conjugated glycopyrronium
(Source: adapted from Table 1-3 and Table 4-1of summary of biopharmaceutic studies)

Table 21. Summary of analytical method validation reports for glycopyrronium quantification in human plasma

Report	Method description and performance	
R0900330C, R0900330C-01	Title: Quantitative determination of NVA237 in human plasma (Li Heparin) by LC-MS/MS	
	LLOQ	1.5pg/mL
	Calibration curve	1.5-500 pg/mL Linear regression, weighting factor: $1/x^2$
	Matrix effect	Mean matrix factor: 1.00 (1.00, 1.01) Precision ≤15%
	Recovery	98.2% (95.4-102.7%) Precision ≤15%
	Intra-day accuracy and precision	Mean bias ≤ 9.6% (11.3% at LLOQ) Precision ≤6.1 % (17.7% at LLOQ)
	Inter-day accuracy and precision	Mean bias ≤6.0% (9.3% at LLOQ) Precision ≤4.3% (10.5% at LLOQ)
	Dilutions	20-fold dilution (up to 1600 pg/mL)
	Stability	Post-preparative stability: 4.5pg/mL at 10ºC for 179.5 hs: mean bias of -1.1%, Precision of 2.9% Freeze-thaw stability (5 cycles) 4.5pg/mL at -15 ºC and -60 ºC : mean bias ≤ -2.0%, Precision ≤ 4.5% 1600 pg/mL at -15 ºC and -60 ºC: mean bias ≤ -5.2%, Precision ≤ 2.2% Stability in spiked human plasma 4.5 pg/mL at RT for 24.25 hours: mean bias -9.6%, Precision 5.3% 1600 pg/mL at RT for 24.25 hours: mean bias -8.6%, Precision 5.3% 4.5 pg/mL at -15 ºC for 449 days: mean bias 5.1%, Precision 4.6% 1600 pg/mL at -15 ºC for 449 days: mean bias -0.6%, Precision 3.7% 4.5 pg/mL at -60 ºC for 449 days: mean bias 0.7%, Precision 3.8% 1600 pg/mL at -60 ºC for 449 days: mean bias -3.8%, Precision 4.2%
R0900330 R0900330-02	Title: Validation of an LC-MS/MS method for the determination of NVA237 in human plasma	
	LLOQ	3.0 pg/mL
	Calibration curve	3.0-2000 pg/mL Linear regression, weighting factor: $1/x^2$
	Matrix effect	Mean matrix factor: 1.00 (0.99, 1.002) Precision ≤15%
	Recovery	70.1% (69.9-70.3%) Precision ≤15%
	Intra-day accuracy and precision	Mean bias ≤ 6.3% (-7.3% at LLOQ) Precision ≤ 8.6% (16.6 % at LLOQ)
	Inter-day accuracy and precision	Mean bias ≤ -3.0% (-4.7% at LLOQ) Precision ≤ 7.9% (14.7% at LLOQ)
	Dilutions	10-fold dilution
	Stability	Post-preparative stability: 9.0 pg/mL at 10ºC for 182 hrs : mean bias 3.1 %, Precision 3.6%

		1600 pg/mL at 10ºC for 182 hrs : mean bias -1.0%, Precision1.9% <u>Stability in spiked human plasma</u> 9.0 pg/mL at -18 ºC for 409 days: mean bias -2.6%, Precision 4.8% 1600 pg/mL at -18 ºC for 409 days: mean bias -5.0%, Precision 2.3%
R0600354A-01 **R0600354A-02**	Quantitative determination of NVA237 in human plasma by LC-MS/MS	
	LLOQ	4.00 pg/mL
	Calibration curve	4.0-2000 pg/mL Linear regression, weighting factor: $1/x^2$
	Matrix effect	Mean matrix factor: 1.5 (1.34-1.66) Precision ≤15%
	Recovery	95.8% (79.0-114%) Precision ≤15%
	Intra-day accuracy and precision	Mean bias ≤ -8.3% (12.5% at LLOQ) Precision ≤6.8% (8.5% at LLOQ)
	Inter-day accuracy and precision	Mean bias ≤7.8% (8.0% at LLOQ) Precision ≤5.3% (6.9% at LLOQ)
	Dilutions	NA
	Stability	<u>Post-preparative stability:</u> 9.0pg/mL at 10ºC for 6 days: mean bias 1.4%, Precision 6.2% 800pg/mL at 10ºC for 6 days: mean bias 3.0%, Precision 3.4% 1800pg/mL at 10ºC for 6 days: mean bias 3.1%, Precision 3.9% <u>Stability in spiked human plasma</u> 9.0 pg/mL at -18 ºC for 34 weeks: mean bias -0.8%, Precision 6.6% 1800 pg/mL at 18 ºC for 34 weeks: mean bias 12.8%, Precision 2.6%

*RT: room temperature

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in the PK samples. As stated in section 2.5.7, the metabolites are not active.

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

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

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 20 presents a summary of analytical methods used for quantification of glycopyrronium and lists out the respective validation report numbers. Details of the main bioanalytical methods are discussed in section 2.9.1.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

In Method R0900330C, the standard curve ranged from 1.5 to 500 pg/mL. A linear regression model, with weighting factor of $1/\text{concentration}^2$ was used for the curve fitting for glycopyrronium.

2.9.5.1 What are the lower and upper limits of quantitation?

In Method R0900330C, LLOQ and ULOQ for glycopyrronium were 1.5 pg/mL and 500 pg/mL, respectively. A 20-fold dilution factor was also validated for 1600 pg/mL

concentration.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical methods for glycopurronim is listed in Table 21.

The selectivity was evaluated by extracting and analyzing blank human plasma from six individual sources both with and without addition of internal standard. All lots were free from significant interfering peaks in the drug and internal standard regions.

2.9.5.3 What is the sample stability under conditions used in the study?

For the bioanalytical Method R0900330C, stability was demonstrated under different conditions as discussed below:

Post-preparative stability
4.5pg/mL on autosampler at 10ºC for 179.5 hours: mean bias of -1.1%, Precision of 2.9%

Freeze-thaw stability (5 cycles)
4.5pg/mL at -15 ºC and -60 ºC: mean bias ≤ -2.0%, Precision ≤ 4.5%
1600 pg/mL at -15 ºC and -60 ºC: mean bias ≤ -5.2%, Precision ≤ 2.2%

Stability in spiked human plasma
4.5 pg/mL at RT for 24.25 hours: mean bias of -9.6%, Precision of 5.3%
1600 pg/mL at RT for 24.25 hours: mean bias of -8.6%, Precision of 5.3%

4.5 pg/mL at -15 ºC for 449 days: mean bias of 5.1%, Precision of 4.6%
1600 pg/mL at -15 ºC for 449 days: mean bias of -0.6%, Precision of 3.7%

4.5 pg/mL at -60 ºC for 449 days: mean bias of 0.7%, Precision of 3.8%
1600 pg/mL at -60 ºC for 449 days: mean bias of -3.8%, Precision of 4.2%

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

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of SEEBRI NEOHALER in geriatric patients is warranted. SEEBRI 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 SEEBRI NEOHALER, 45% were aged 65 and older, while 10% 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

(b) (4) SEEBRI NEOHALER should (b) (4) be used (b) (4) in patients with severe renal impairment (estimated GFR less than 30 mL/min/1.73m^2), including those with end-stage renal disease requiring dialysis. ~~, 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

No dose adjustment is required for patients with hepatic impairment. The effects of hepatic impairment on the pharmacokinetics of glycopyrrolate were not studied *[see Clinical Pharmacology (12.3)]*.

12.2 Pharmacodynamics

(b) (4)

(b) (4)

Cardiac Electrophysiology (b) (4): The effect of SEEBRI NEOHALER on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled double-blind, single-dose, crossover thorough QTc study in 73 healthy subjects. At the dose 16-fold the therapeutic daily dose, SEEBRI NEOHALER did not prolong QTc to any clinically relevant extent. (b) (4)

12.3 Pharmacokinetics
Linear pharmacokinetics of glycopyrrolate was observed following inhalation of daily doses of 31.2 mcg to 249.6 mcg.

Absorption: Following oral inhalation using the SEEBRI NEOHALER inhaler, glycopyrrolate was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of glycopyrrolate inhaled via SEEBRI NEOHALER was estimated to be about 40%. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption. (b) (4)

Following repeated once-daily inhalation in patients with COPD, PK steady-state of glycopyrrolate was reached within 1 week of treatment. There was no indication that the glycopyrrolate pharmacokinetics changes over time.

Distribution: After intravenous administration, the steady-state volume of distribution of glycopyrrolate was 83 L and the volume of distribution in the terminal phase 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: In vitro metabolism studies show glycopyrrolate hydroxylation resulting in a variety of mono- and bishydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9). Further in vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrrolate and the hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family pre-systemically and/or via first pass metabolism from the swallowed dose fraction of orally inhaled glycopyrrolate.

(b) (4)

(b) (4)

- Glucuronide and/or sulfate conjugates of glycopyrrolate were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

(b) (4)

Elimination: (b) (4)

Renal elimination of parent drug accounts for about 60% to 70% of total clearance of systemically available glycopyrrolate whereas non-renal clearance processes account for about 30% to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 62.4 mcg and 249.6 mcg glycopyrrolate by healthy volunteers and patients with COPD, mean renal clearance of glycopyrrolate was in the range of 17.4 L/h and 24.4 L/h indicating active tubular secretion contributes to the renal elimination of glycopyrrolate. (b) (4)

Glycopyrrolate plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life was much longer after inhalation (33 to 53 (b) (4) hours) than after intravenous (6.2 hours) and oral (2.8 hours) administration. (b) (4)

Drug Interactions: 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 systemic 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 relevant effect of age (40 to 85 years) or body weight (45 to 120 kg) on systemic exposure to glycopyrrolate. In addition, there was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, Hispanic/Latino, Japanese subjects). Gender, smoking status, and baseline FEV1 have no apparent effect on maximal or average glycopyrrolate systemic exposure.

(b) (4)

Renal Impairment: Renal impairment has an impact on the systemic exposure to glycopyrrolate. A moderate mean increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment [estimated glomerular filtration rate (GFR) greater than or equal to 30 mL/min/1.73m^2] and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease [estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73m^2] (b)

(b) (4)

-*Use in Specific Populations (8.6)]*.

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 (b) (4)

4. Appendix

4.1 Appendix –PM Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

NDA Number	207923
Brand Name	SEEBRI NEOHALER
Drug Components	Glycopyrrolate
Proposed dosing	15.6 mcg glycopyrrolate (equivalent to12.5 mcg glycopyrronium), BID
Pharmacometrics Reviewer	Lei He, Ph.D. Dinko Rekic, 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 questions.

Are there any covariates that influence the systemic exposure of glycopyrronium?
eGFR and body weight, were identified as significant intrinsic physiological factors contributing to the inter-individual variability in CL/F of glycopyrronium. The effect of age on CL/F of glycopyrronium can be explained by decreasing eGFR with age. Gender, smoking status, and baseline FEV1 had no apparent effect on glycopyrronium systemic exposure following NVA237 inhalation. No dependence of CL/F on ethnicity was detected.

For these exposure differences, no dosing adjustments are recommended.

Can the recommended dosing regimen, NVA237 12.5 mcg BID, be used in patients with mild and moderate renal impairment (RI)?
In Study NVA237A2105, following a single NVA237 inhalation (100 mcg), the AUClast of glycopyrronium in patients with mild, moderate, server RI and ESRD were 1.42, 1.02, 2.21, and 2.07 fold higher compared to healthy subjects, respectively. Cmax of glycopyrronium were similar or even lower in RI patients. The renal clearance of glycopyrronium in subjects with RI reduced to be 62%, 46%, and 20% of that in healthy subjects. Therefore, it was concluded that the recommended dose, 12.5 mcg BID, can be used in chronic obstructive pulmonary disease (COPD) patients with mild and moderate RI.

Simulation of glycopyrronium steady state exposure indicated that, for patients with mild to moderate RI ($30 \leq eGFR \leq 80$), the glycopyrronium steady-state exposure following NVA237 12.5 mcg BID dosing did not exceed the exposure in COPD patients without RI receiving NVA237 25 mcg BID. For patients even with end stage renal disease ($eGFR<30$ mL/min/1.73 m^2), the simulated exposure was well below the safety threshold of 2960 pg*h/mL established based on the 200 mcg once daily regimen found to be safe in the 28-day safety study CNVA237A2206. Therefore, the recommended dose can be used in COPD patients with mild and moderate RI, which is consistent with the conclusion of the dedicated PK study in patients with RI.

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

Linear pharmacokinetics of glycopyrrolate was observed following inhalation of daily doses of 31.2 mcg to 249.6 mcg.

Absorption: Following oral inhalation using the SEEBRI NEOHALER inhaler, glycopyrrolate was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of glycopyrrolate inhaled via SEEBRI NEOHALER was estimated to be about 40%. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption. (b) (4)

Following repeated once-daily inhalation in patients with COPD, PK steady-state of glycopyrrolate was reached within 1 week of treatment. There was no indication that the glycopyrrolate pharmacokinetics changes over time.

Distribution: After intravenous administration, the steady-state volume of distribution of glycopyrrolate was 83 L and the volume of distribution in the terminal phase 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: In vitro metabolism studies show glycopyrrolate hydroxylation resulting in a variety of mono- and bishydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9). Further in vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of glycopyrrolate and the hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family pre-systemically and/or via first pass metabolism from the swallowed dose fraction of orally inhaled glycopyrrolate.

(b) (4)

-Glucuronide and/or sulfate conjugates of glycopyrrolate were found in urine of humans after repeated inhalation, accounting for about 3% of the dose.

(b) (4)

Elimination: (b) (4)

Renal elimination of parent drug accounts for about 60% to 70% of total clearance of systemically available glycopyrrolate whereas non-renal clearance processes account for about 30% to 40%. Biliary clearance contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

Following inhalation of single and repeated once-daily doses between 62.4 mcg and 249.6 mcg glycopyrrolate by healthy volunteers and patients with COPD, mean renal clearance of glycopyrrolate was in the range of 17.4 L/h and 24.4 L/h indicating active tubular secretion contributes to the renal elimination of glycopyrrolate. (b) (4)

Glycopyrrolate plasma concentrations declined in a multi-phasic manner. The mean terminal elimination half-life 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: 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 systemic 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 relevant effect of age (40 to 85 years) or body weight (45 to 120 kg) on systemic exposure to glycopyrrolate. In addition, there was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, Hispanic/Latino, Japanese subjects). Gender, smoking status, and baseline FEV1 have no apparent effect on maximal or average glycopyrrolate systemic exposure.

(b) (4)

Renal Impairment: Renal impairment has an impact on the systemic exposure to glycopyrrolate. A moderate mean increase in total systemic exposure (AUClast) of up to 1.4-fold was seen in subjects with mild and moderate renal impairment [estimated glomerular filtration rate (GFR) greater than or equal to 30 mL/min/1.73m^2] and up to 2.2-fold in subjects with severe renal impairment and end stage renal disease [estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73m^2]. (b) (4)

se in Specific Populations (8.6)].

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 (b) (4)

SUMMARY OF SUBMISSION

Novartis has submitted NDA 207923 seeking the marketing approval for Glycopyrrolate Inhalation Powder (SEEBRI NEOHALER), which is indicated 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 16 clinical pharmacology studies, of which 5 studies have also been submitted to support NDA 207930 (QVA149, Indacaterol /Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis).

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.

Please note that NVA237 12.5 mcg glycopyrronium is used throughout this review and is equivalent to NVA237 15.6 mcg glycopyrrolate. NVA237 is used in reference to the formulation and dosing. Doses of NVA237 and biofluid concentrations refer to glycopyrronium, the quaternary ammonium ion ('active moiety') of NVA237.

A total of five population PK study reports were submitted in this NDA (Table 1).

In [NVA237 renal impairment modeling], a NVA237 population PK model was developed to assess the effect of the renal impairment on the NVA237 PK and simulate the NVA237 steady state exposure in patients with renal impairment taking NVA237 50 mcg QD or 12.5 mcg BID ([NVA237 renal-impairment simulation]). The [NVA237 renal impairment modeling] and [NVA237 renal-impairment simulation] were summarized in Section 4.1.1.

In [NVA237 PopPK modeling low dose], the model was derived from an existing model which was developed in [NVA237 PopPK modeling] with additional data from Study CNVA237A2317 and A2318 using 12.5 mcg BID regimen added. In [NVA237 PopPK simulation J-NDA], the model developed in [NVA237 PopPK modeling] was used to perform simulation for assessment of the effect of ethnicity (Japanese vs. non-Japanese) and smoking status on the NVA237 PK, which was also covered by [NVA237 PopPK modeling low dose]. Therefore, [NVA237 PopPK modeling low dose], but not [NVA237 PopPK modeling] and [NVA237 PopPK simulation J-NDA] was summarized in Section 4.1.2.

Table 1. Summary of population PK study reports submitted in NDA207923

Report ID	Study Title	Data Source
NVA237 renal impairment modeling	Population Pharmacokinetic Modeling of NVA237: Assessment of the effect of renal Impairment on the NVA237 PK from studies CNVA237A2103 and CNVA237A2105	CNVA237A2103 (25, 50, 100, 200mcg, QD); CNVA237A2105 (100 mcg QD)
NVA237 renal-	Predicted steady state exposure in patients	The model developed in report

impairment simulation	with renal impairment taking NVA237 12.5 mcg twice daily	"NVA237 renal impairment modeling" was used for simulation.
NVA237 PopPK modeling low dose	Population pharmacokinetics of NVA237 12.5 microgram twice daily in COPD patients	CNVA237A2103(25, 50, 100, 200mcg, QD); CNVA237A2303 and A2304 (50mcg, QD); CNVA237A2317 and A2318 (12.5mcg, BID)
NVA237 PopPK modeling	Population Pharmacokinetic Modeling and Covariate Analysis of NVA237: Pooling studies CNVA237A2103, CNVA237A2303, CNVA237A2304	CNVA237A2103(25, 50, 100, 200mcg, QD); CNVA237A2303 and 2304(50mcg, QD)
NVA237 PopPK simulation J-NDA	Population Pharmacokinetic Simulation: Assessment of the Effect of Ethnicity (Japanese vs. non-Japanese) and Smoking Status on the NVA237 Pharmacokinetics	The model developed in report "NVA PopPK modeling" was used for simulation.

4.1.1 ASSESSMENT OF THE EFFECT OF RENAL IMPAIRMENT ON THE NVA237 PK AND PREDICTED STEADY STATE EXPOSURE IN PATIENTS WITH RENAL IMPAIRMENT TAKING NVA237 12.5 MCG TWICE DAILY

The population PK analysis conducted by the sponsor and main conclusions reached from this analysis in reports of [NVA237 renal impairment modeling] and [NVA237 renal-impairment simulation] are summarized in this section.

Objectives

- To develop a population PK model for NVA237 in patients with RI.
- To use the model and simulate the steady state exposure (AUCtau) of NVA237 in patients as a function of the degree of RI (characterized by eGFR) at 50 and 200 mcg QD.

Software

The analysis was performed using the nonlinear mixed effects modeling (NONMEM) software system, NONMEM VI version 2.

Data Source

Data from 2 studies were pooled for the population PK analysis, including Study CNVA237A2103 and Study CNVA237A2105 (Table 2). In both studies rich PK sampling was performed. The demographics of subjects from two studies were summarized in Tables 3 and 4.

Table 2. Description of NVA237 studies and PK data

Study Number and Title	Dose (µg)	Sample Size (N)	PK Sampling Design	Sampling Day	Assay Method and LLOQ
CNVA237A2103: A multi-center, randomized, double-blind, parallel-group study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple inhaled NVA237 doses at four dose levels in COPD patients.	25 50 100 200	Total = 33 25µg (N=8) ; 50µg (N=8) ; 100µg (N=8) ; 200µg (N=9)	pre-dose, 5, 15, 30 min., and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose and additional samples at 36 and 48 hours post-dose on Day 14. Trough collected on Days 2, 5, 7 and 9.	1, 2,5,7,9, 14	LC-MS-MS 4pg/mL
CNVA237A2105: An open label, non-randomized, parallel-group study to characterize and compare the pharmacokinetics, safety, and tolerability of a single dose of NVA237 in subjects with mild, moderate, severe and end-stage renal impairment with that in matched healthy control subjects.	100	Total = 48 HV (N=18) ; Mild (N=8) ; Moderate (N=8) ; Severe (N=8) RI Subjects and ESRD (N=6) ESRD on dialysis (N=5)	Period 1: Pre-dose, 5, 10, 15, 30 min., and 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours post-dose for healthy volunteers, subjects with mild, moderate and severe RI and subjects with ESRD (up to 72hr post-dose only) Period 2: Pre-dose, 5, 10, 15, 30 min., and 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, 48 and 72 hours post-dose for subjects with ESRD on dialysis.	1 ,2,3, 4 1, 2,3	LC-MS-MS 4pg/mL

(Source: Table 3-1, NVA237 renal impairment modeling report)

Table 3. Demographics of Study CNVA237A2103

Study CNVA237A2103 Demographics	Mean ; Median (Standard Deviation) [Min – Max]	
Age (yrs)	61 ; 63 (8.03) [43.09 – 73.01]	
Weight (kg)	77.35 ; 78.3 (12.22) [50.4 – 105.9]	
Gender	N=19 Males	N=14 Females
Race	N = 33 Caucasians	
GFR ($mL/min/1.73m^2$)	73.25 ; 71.8 (10.10) [52.7 – 94.6]	

(Source: Table 5-1, NVA237 renal impairment modeling report)

Table 4. Demographics of Study CNVA237A2105 as a function of renal impairment categories in comparison with healthy volunteers

	Mean ; Median (Standard Deviation) [Min – Max]			
Study CNVA237A2105 Demographics	Healthy volunteer (eGFR > 80 mL/ $min/1.73m^2$)	Mild renal impairment (50 ≥ eGFR ≤ 80 $mL/min/1.73m^2$)	Moderate renal impairment (30 ≥ eGFR < 50 $mL/ min/1.73m^2$)	Severe renal impairment (eGFR < 30 $mL/min/1.73m^2$)
Age (yrs)	55 ; 58 (11.05) [30 – 70]	59 ; 57 (6.48) [52 – 69]	60 ; 57 (8.34) [48 – 70]	55 ; 58 (10.17) [35 – 70]
Weight (kg)	81.64 ; 78 (10.79) [68.3 – 108.9]	82.63 ; 77.15 (12.22) [67 – 99.7]	85.65 ; 86.1 (9.80) [66.1 – 100.5]	85.36 ; 86.75 (12.71) [58 – 104.5]
Gender	N=12 Males N=6 Females	N=4 Males N=4 Females	N=3 Males N=5 Females	N=10 Males N=4 Females
Race	N=18 Caucasians	N=8 Caucasians	N=8 Caucasians	N=14 Caucasians
GFR ($mL/min/1.73m^2$)	95.69 ; 92.52 (12.98) [81.04 – 134.25]	59.02 ; 55.66 (9.98) [50.48 – 75.66]	42.65 ; 43.19 (5.71) [33.89 – 48.91]	15.86 ; 12.17 (9.67) [4.80 – 29.38]

Note: Severe renal impairment group includes 6 (six) patients with ESRD.

(Source: Table 5-2, NVA237 renal impairment modeling report)

Population PK Model Development

Structural Model

Two- and three- compartment models following instantaneous input, 1st-order transfer to and from the peripheral compartment to the central compartment, and 1st-order elimination from the central compartment, 1st-order transfer to and from the 2nd-peripheral compartment to the central compartment were fitted to the NVA237 plasma concentration time profile observed. Random-effects (η) in the structural model were used to quantify variance and covariance of between-subject variability (BSV) in fixed-effect parameters and were assumed to be multiplicative and log-normally distributed. The residual unexplained variability (RUV) was modeled with proportional and additive error components.

Covariate Model Development

The demographic and physiological variables tested as covariates on the structural PK models parameters included: age (AGE, yrs), body-weight (BWT, kg), gender (SEX), estimated glomerular filtration rate (eGFR, mL/min/1.73m^2) and lean-body-weight (LBW, kg). Scatter-plot of demographic and physiological variables shows the correlation among covariates: with increase in AGE (yrs), renal function (GFR, mL/min/m2) declines; body-weight (WT0, kg) and lean-body-weight (LBW, kg) are correlated (Figure 1).

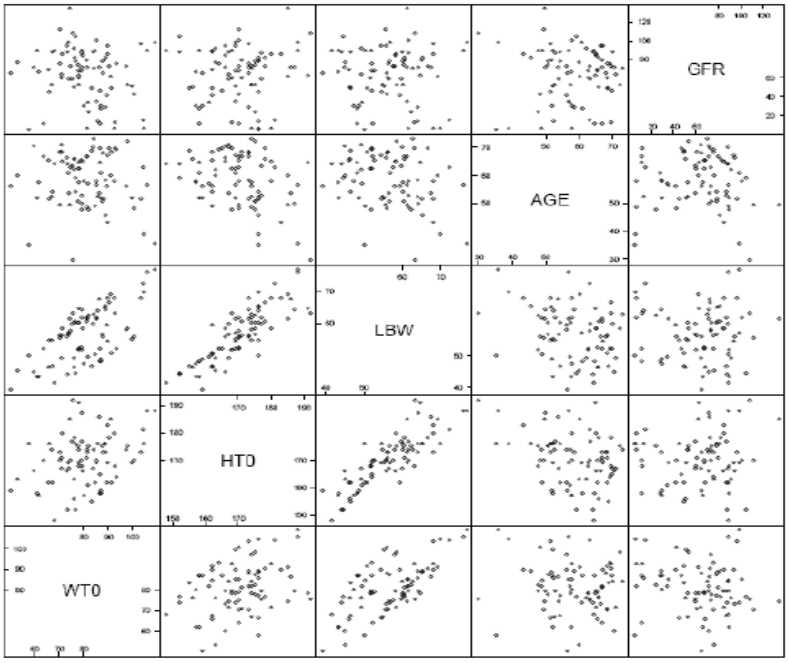


Figure 1. Scatter-Plot Matrix of Demographic and Physiological Variables from the Population PK dataset
(Source: Figure 4-4, NVA237 renal impairment modeling report)

Covariate modeling was performed using a stepwise process, (i) visual inspection of the posthoc random-effects (ETAs) versus likely covariates, (ii) physiological plausibility and (iii) statistically significant drop-in objective-function-value when the covariate is

included in the model. The "typical value" of clearance (TVCL/F) was modeled as the sum of non-renal (CL_{NR}/F) and renal (CL_R/F) clearance, where CL_R/F was assumed to be proportional to GFR. The typical value of clearance for a "normal" patient with GFR = 90 mL/min/1.73m^2 was modeled as follows: $TVCL/F = CL_{NR}/F + CL_R/F \times (GFRi/90)$.

Final Model Evaluation

Model adequacy was primarily evaluated based on visual inspection of different diagnostic plots and precision of the parameter estimates. Visual predictive check (VPC) and posterior predictive check (PPC) were performed for model evaluation.

Prediction of Steady State Exposure

The developed model was used to simulate the steady state exposure of glycopyrronium in patients with RI taking NVA237 50 mcg QD (in report of [NVA237 renal impairment modeling]) and 12.5 mcg BID (in report of [NVA237 renal-impairment simulation]). Only the simulation in patients with RI taking 12.5 mcg BID dosing regimen was summarized in this review.

For the simulations, eGFR for each individual was calculated based on the MDRD formula adjusted for body surface area: First, unadjusted eGFR were calculated according to the MDRD formula, represented as

$$eGFR_i = 175 * (SCR_i / 88.4)^{-1.154} * AGE_i^{-0.203} * [1.212 if Black] * [0.742 if Female]$$

where $eGFR_i$ is the estimated glomerular filtration rate in individual i, SCR_i its serum creatinine (μmol/L), and AGE_i its age (years). The body surface area of each subject was calculated as

$$BSA_i = \exp(-3.751) * HT_i^{0.422} * WT_i^{0.515}$$

where HTi and WTi are the height in cm and weight in kg of subject i, respectively. The body surface adjusted glomerular filtration rate was then determined as

$$eGFR_{sim,i} = eGFR_i * BSA_i / 1.73.$$

Covariate values (eGFR and body weight) were generated based on the study population from CNVA237A2103 and CNVA237A2105 to represent cohorts of patients with different renal function as well as a cohort representing typical COPD patients. PK parameters were sampled based on the population distribution of the model parameters taking into account the sampled covariates. Based on these individual parameter vectors, PK profiles of 1000 virtual patients were simulated who received 12.5 mcg NVA237 BID via inhalation. The exposure metric, AUC0-24h at steady state, was computed from the PK profiles and summarized in plots and tables as a function of eGFR. The distribution was then compared to reference values derived from simulations of COPD patients receiving daily doses of 50mcg or 200mcg, respectively. The higher 200 mcg daily dose was selected since in the 28-day safety study CNVA237A2206 in COPD patients, doses of 100 and 200 mcg of NVA237 were found to be safe, i.e. the corresponding exposure serves as safety threshold.

Results

Final Model

A three-compartment mamilliary structural PK model fitted the overall concentration time data reasonably well. Two major covariates, GFR and BWT were identified as intrinsic physiological factors contributing to the inter-individual variability in CL/F and V1/F respectively. The fraction of total CL/F in the final model which depends on renal function in a typical subject with normal renal function (GFR = 90 mL/min/1.73m^2) is 69%. Bioavailability following inhalation delivery was assumed to be unity. The description of the final population PK model parameters and their 95% confidence intervals was shown in Table 5.

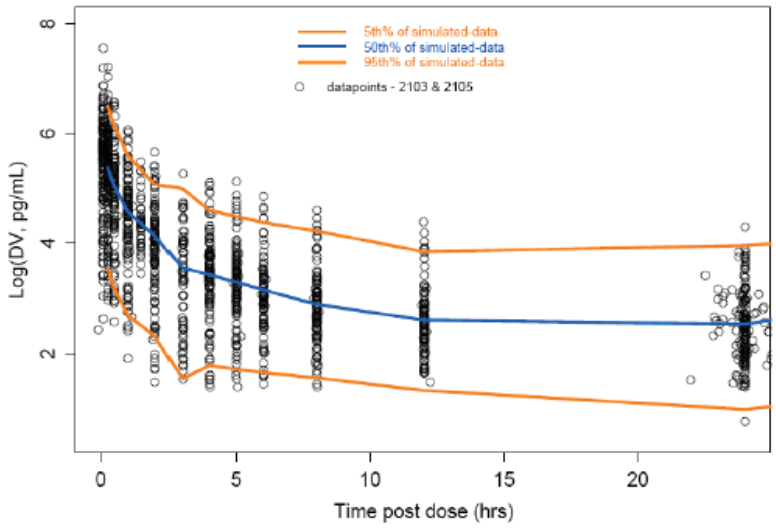
Table 5. Final population PK model parameter estimate and 95% CI

Description	Units	Point Estimate (95% CI)	Variance (ω) (95% CI)
Apparent renal clearance (CL_R/F) of a typical patient with healthy renal function (GFR = 90 mL/min/m^2)	L/hr	82.5 (52.7 – 112)	0.132 (0.076 – 0.188)
Apparent non-renal clearance (CL_{NR}/F) for a typical patient	L/hr	37.2 (16.6 – 57.9)	
Apparent central volume (V1/F) of distribution for a typical patient with BWT=80 kg.	L	315 (283 – 347)	0.216 (0.157 – 0.275)
Apparent peripheral volume (V2/F) of distribution for a typical patient.	L	2670 (2251 – 3089)	0.284 (0.159 – 0.409)
Apparent inter-compartmental clearance (Q2/F) for a typical patient	L/hr	157 (137 – 177)	0.319 (0.191 – 0.447)
Apparent inter-compartmental clearance (Q3/F) for a typical patient	L/hr	151 (112 – 190)	N.E.
Apparent peripheral volume (V3/F) of distribution for a typical patient	L	156 (132.1 – 179.9)	N.E.
Fractional bioavailability of 25µg dosing cohort	Unitless	0.786 (0.729 – 0.843)	N.E.
$\Theta_{proportional}$	-	0.186 (0.152 – 0.22)	
$\Theta_{additive}$	pg/mL	1.84 (1.11 – 2.58)	

Note: 95% CI were calculated from the standard error (SE) i.e. 1.96*SE ± point estimate.
Omega (ω) is the variance estimate of the population parameter variability (PPV);
N.E. – not estimated.
(Source: Figure 5-3, NVA237 renal impairment modeling report)

Model Evaluation

Visual predictive check (VPC) was conducted on the final model: two-hundred datasets were simulated using the final model parameter estimates in Perl Speaks Nonmem and the simulated 5th, 50th and 95th percentiles were overlaid on the observed data from studies CNVA237A2103 and CNVA237A2105. The model mimics the overall trend and variability in the population data (Figure 2).

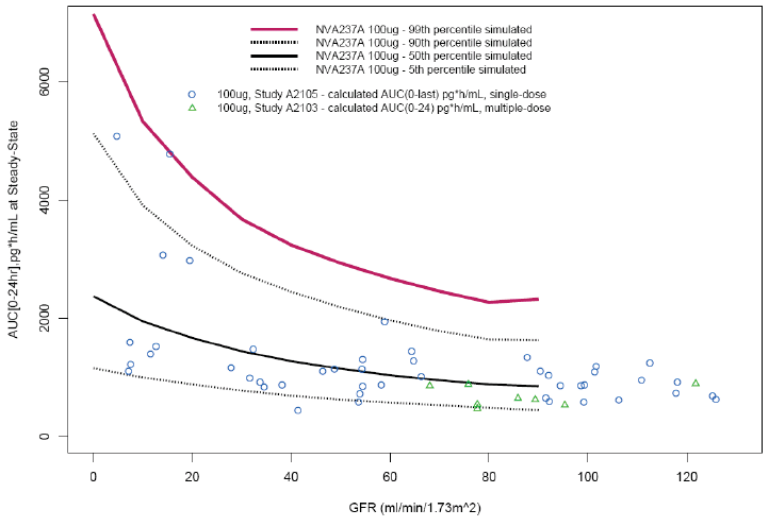


Source:/CNVA237A/pool/pkpd_002/nonmem/PK_02_05_RI2_rmESRD_dialysis/PK_Model_5_VPC.pdf

Figure 2. Visual Predictive Check, comparing the final model prediction of concentration (Log(DV), pg/mL)-time post-dose data overlaid with the single and multiple dose data from study CNVA237A2103 and single dose data from study CNVA237A2105

(Source: Figure 5-1, NVA237 renal impairment modeling report)

A posterior predictive check (PPC) was performed using the final model. The predicted posterior distribution of AUC0-24h was calculated from the individual simulated concentration time (0-24hr, hourly sampling) post 100µg dose at steady-state and overlaid on the calculated AUC0-last and AUC0-24h from study CNVA237A2105 and 100mcg dose from CNVA237A2103, respectively, as a function of GFR (mL/min/1.73m2). The simulated posterior distribution (5th, 50th, 95th and 99th) of AUC0-24h for 100mcg dose overlapped all calculated AUC0-last from patients in study CNVA237A2105 as a function of GFR.



Source:/CNVA237A/pool/pkpd_002/nonmem/PK_02_05_RI2_rmESRD_dialysis/pk_100µgRI_PPC.pdf

Figure 3. Posterior Predictive Check, comparing the final model predicted AUC0-24h at steady-state following 100mcg dosing with the calculated AUC0-last and AUC0-24h from the observed concentration time data from Study CNVA237A2105 and Study CNVA237A2103, respectively, as a function of GFR.

(Source: Figure 5-2, NVA237 renal impairment modeling report)

Simulation of Glycopyrronium Steady State Exposure in RI Patients Taking NVA12.5 mcg BID

The simulated exposure from n=1000 patients receiving NVA237 12.5 mcg BID by inhalation as a function of eGFR was summarized in Table 6 and visualized by plotting the 5%, 50% and 99% percentile (Figure 4 and Figure 5). The simulated steady-state exposure in COPD patients on different regimens of NVA237 was summarized in Table 7.

For patients with mild to moderate RI ($30 \leq eGFR \leq 80$), steady-state exposure for 12.5 mcg BID dosing did not exceed that of COPD patients without RI receiving 25 mcg BID (the 99th exposure percentile of a 25 mcg BID dose was 1204 pg*h/mL).

Even for patients with end stage renal disease (eGFR<30 mL/min/1.73 m^2), the simulated exposure was well below the safety threshold of 2960 pg*h/mL established based on the 200 mcg once daily regimen found to be safe in the 28-day safety study CNVA237A2206.

Table 6. Steady-state AUC0-24h (pg*h/mL) as a function of eGFR for 12.5 mcg BID in comparison to COPD patients

eGFR (mL/min/1.73 m^2)	(1st %)	(5th %)	(10th %)	(50th %)	(90th %)	(95th %)	(99th %)
0	222.1	296.7	347.3	611.9	1114.7	1322.9	1845.9
10	193.6	256.9	296.5	502.4	878.7	1009.4	1364.4
20	176.5	224.9	253.6	427.8	718.6	828.0	1119.8
30	153.9	198.1	222.8	369.9	615.3	708.7	946.3
40	133.3	175.6	198.5	325.7	547.9	626.9	832.6
50	118.9	159.2	178.1	293.4	491.7	556.9	750.8
60	111.1	145.1	161.4	264.3	445.2	501.3	689.7
70	103.5	133.3	149.3	242.1	406.9	456.0	633.1
80	96.1	122.8	137.8	224.4	373.0	421.7	584.2
90	87.5	113.5	127.4	207.7	347.9	392.2	542.0
73.2 ± 10.0 (COPD[1])	99.2	128.0	142.8	240.0	409.4	471.6	598.2
81.9 ± 13.7 (COPD[2])	91.1	112.9	132.3	223.9	378.1	427.6	601.9

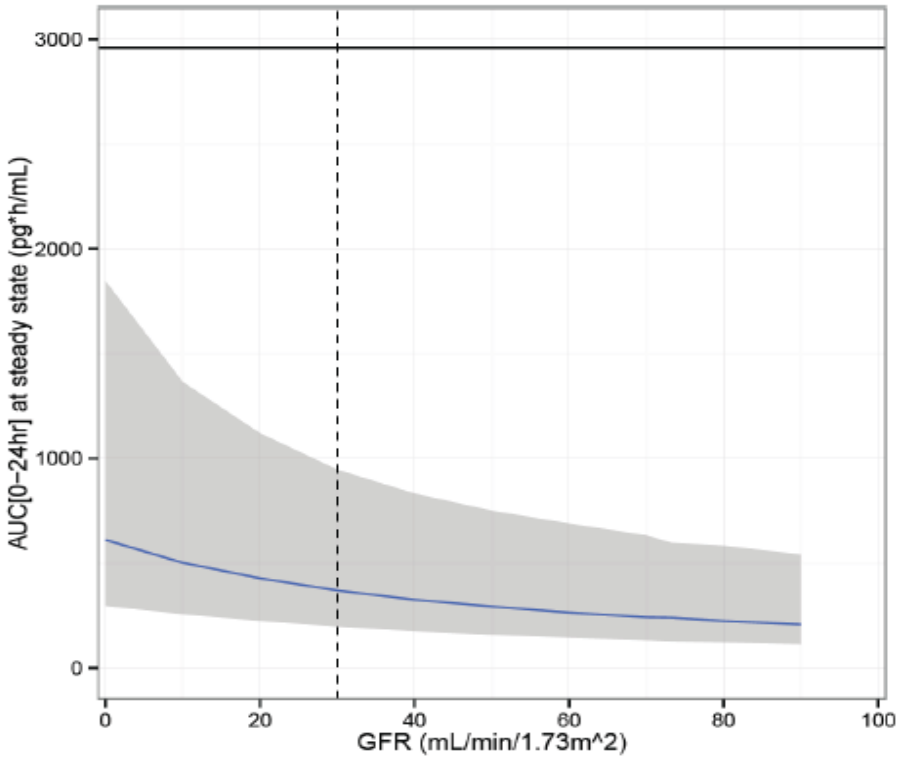
1st, 5th, 10th, 50th, 90th, 95th, 99th percentile of steady-state AUC0-24h (pg*h/mL) from N=1000 simulated patients as a function of eGFR following 12.5mcg twice-daily dosing. [1,2] Simulated reference cohort representing COPD patients following NVA237 12.5mcg twice-daily dosing with eGFR estimated with(2) or without(1) adjustment for body surface area, respectively. Source: vob/CNVA237A/pool/pkpd_003/nonmem/BID2/sim1/sim2.csv.

(Source: Table 5-1, NVA237 renal-impairment simulation report)

Table 7. Simulated steady steady-state AUC0-24h (pg*h/mL) in COPD patients on different regimens of NVA237

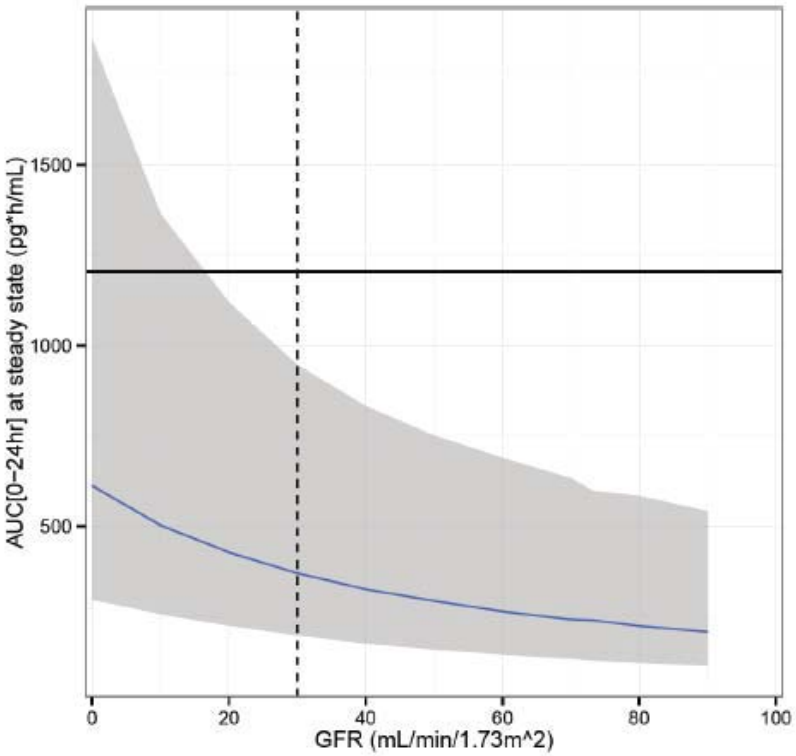
Regimen	(1st %)	(5th %)	(10th %)	(50th %)	(90th %)	(95th %)	(99th %)
12.5mcg b.i.d.	91.1	112.9	132.3	223.9	378.1	427.6	601.9
25mcg b.i.d.	182.3	225.7	264.5	447.8	756.3	855.2	1203.8
200mcg q.d.	717.8	888.6	1037.6	1760.3	2958.3	3347.8	4716.5

1st, 5th, 10th, 50th, 90th, 95th, 99th percentile of steady-state AUC0-24h (pg*h/mL) from a simulated reference cohort (N=1000) representing COPD patients with a mean eGFR of 82 (13.7) mL/min/1.73 m^2 (mean and standard deviation). Source: vob/CNVA237A/pool/pkpd_003/nonmem/BID2/sim1/sim1.csv and vob/CNVA237A/pool/pkpd_003/nonmem/BID2/sim1/sim2.csv.
(Source: Table 5-2, NVA237 renal-impairment simulation report)



Results from simulating cohorts of 1000 patients with varying degrees of renal impairment receiving 12.5mcg b.i.d.. The band is the 5th, 50th and 99th percentile of the patients with renal impairment. The horizontal line is the safety threshold of 2960 pg h/mL [PopPK_NVA237_Assessment_of_the_effect_of_renal_impairment], which was equal to the 90th exposure percentile of a 200 mcg once daily dose derived from study CNVA237A2105. The vertical line separates patients with severe renal impairment (eGFR<30mL/min/1.73m^2) from those with less or no renal impairment. Source: vob/CNVA237A/pool/pkpd_003/nonmem/BID2/sim1/plot2.pdf.

Figure 4. Steady-state AUC0-24h as a function of eGFR for 12.5 mcg BID in comparison to 200 mcg QD in COPD patients
(Source: Figure 5-1, NVA237 renal-impairment simulation report)



Results from simulating cohorts of 1000 patients with varying degrees of renal impairment receiving 12.5mcg b.i.d. and 1000 simulated COPD patients that received 25 mcg b.i.d. The band is the 5th, 50th and 99th percentile of the patients with renal impairment. The horizontal line is the 99th percentile of the COPD patients receiving the 50 mcg daily dose. The vertical line separates patients with severe renal impairment (eGFR<30mL/min/1.73m^2) from those with less or no renal impairment. Source: vob/CNVA237A/pool/pkpd_003/nonmem/BID2/sim1/plot2.pdf.

Figure 5. Steady-state AUC0-24h as a function of eGFR for 12.5 mcg BID in comparison to 25 mcg BID in COPD patients
(Source: Figure 5-2, NVA237 renal-impairment simulation report)

Conclusions

- A three-compartment mamilliary PK model with instantaneous absorption, 1st-order transfer from the systemic-circulation to peripheral-compartment 1 and 2 and 1st-order transfer from peripheral-compartments to systemic-circulation and elimination from systemic-circulation following inhalation delivery adequately characterized the systemic exposure of NVA237.
- Two major covariates, eGFR and BWT, were identified as intrinsic physiological factors contributing to the inter-individual variability in CL/F and Vc/F, respectively.
- For patients even with completely inhibited renal function (eGFR=0 mL/min/1.73 m^2), following NVA237 12.5 mcg BID dosing regimen, the simulated glycopyrronium systemic exposure at steady state remained below the safety threshold of 2960 pg*h/mL, which was established following 200 mcg QD dosing regimen and found to be safe in the 28-day safety study CNVA237A2206.
- For patients with mild and moderate RI (eGFR≥30 mL/min/1.73m^2), the total systemic exposure (AUC0-24h) following NVA237 12.5 mcg BID dosing

remained smaller than the exposure in COPD patients taking a 50 mcg QD dose studied in the phase III studies CNVA237A2303 and CNVA237A2304.

- It is concluded that NVA237 can be used at the recommended dose (12.5 mcg BID) in COPD patients with mild and moderate RI (eGFR≥30mL/min/1.73 m^2).

4.1.2 POPULATION PHARMACOKINETICS OF NVA237 12.5 MICROGRAM TWICE DAILY IN COPD PATIENTS

The population PK analysis conducted by the sponsor and main conclusions reached from this analysis in report of [NVA237 PopPK modeling low dose] are summarized in this section.

Objectives

- Evaluate the PK of glycopyrronium following inhalation of NVA237 12.5 mcg BID and compare to NVA237 50 mcg QD.
- Quantify identified dependence of average steady state exposure (CL/F) of glycopyrronium on body weight and age for COPD patients receiving NVA237 12.5 mcg BID.
- Explore dependence of PK on selected demographic covariates.

Software

The analysis was performed using the nonlinear mixed effects modeling (NONMEM) software system, NONMEM VII version 2.

Data Source

Data from 5 clinical studies including 1 phase 1 study using 25, 50, 100 and 200 mcg QD regimens, 2 phase 3 studies using 50 mcg QD regimen, and 2 phase 3 studies using 12.5 mcg BID regimen, were pooled in the NVA237 population PK analysis (Table 8). Demographic baseline covariates were summarized by study in Tables 9 and 10.

Table 8. Studies and evaluable PK data included in the analysis

Study Number and Title	Dose (µg) and Regimen	Sample Size (N)[1]	Sampling Day	PK Sampling Design	Assay Method and LLOQ
[Study CNVA237A2103]: A multi-center, randomized, double-blind, parallel-group study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple inhaled NVA237 doses at four dose	25 o.d. 50 o.d. 100 o.d. 200 o.d.	Total = 33 25µg (N=8); 50µg (N=8);	1, 2,5,7,9, 14	pre-dose, 5, 15, 30 min., and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose and additional samples at 36 and 48 hours post-dose on Day 14. Trough	LC-MS-MS 4pg/mL

levels in COPD patients.		100µg (N=8); 200µg (N=9)		samples collected on Days 2, 5, 7 and 9.	
[Study CNVA237A2303]: A 52-week treatment, randomized, double-blind, placebo-controlled, with open-label tiotropium, parallel-group study to assess the efficacy, safety and tolerability of NVA237 in patients with chronic obstructive pulmonary disease.	50 o.d.	Total = 130	1, 2, 15, 85, 86, 183, 365, 366	1, 2, 15 min and 1, 3, 4, 23h15min post-dose -15 min, 1, 2, 15 min. and 1h post-dose -15 min, 5, 15 min and 1, 3, 4, 23h15min post-dose -25 min, 5, 15 min and 1h post-dose -25 min, 15 min and 1, 23h15min post-dose	LC-MS-MS 3pg/mL
[Study CNVA237A2304]: A 26-week treatment, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety and tolerability of NVA237 in patients with chronic obstructive pulmonary disease.	50 o.d.	Total = 167	1, 2, 15, 85, 86, 183, 184	1, 2, 15 min. and 1, 3, 4, 23h15min post-dose -25 min, 1, 2, 15 min. and 1h post-dose -25 min, 5, 15 min. and 1, 3, 4, 23h15min post-dose -25 min, 5, 15 min. and 1, 23h15min post-dose	LC-MS-MS 3pg/mL
[Study CNVA237A2317]: A 12-week multi-center, randomized, double-blind, placebo controlled study to assess the efficacy and safety of NVA237 twice daily in stable COPD patients	12.5 µg b.i.d.	Total = 46	29, 85	-25, 2, 20, 55 min, 3h50min, 5 h	LC-MS-MS 1.5pg/mL
[Study CNVA237A2318]: A 12-week multi-center, randomized, double-blind, placebo controlled study to assess the efficacy and safety of NVA237 twice daily in stable COPD patients	12.5 µg b.i.d.	Total = 31	29, 85	-25, 2, 20, 55 min, 3h50min, 5 h	LC-MS-MS 1.5pg/mL

[1] Subjects with evaluable PK data that were included in the population PK analysis.

(Source: Table 3-1, NVA237 PopPK modeling low dose Report)

Table 9. Summary of continuous covariates by study

Covariate	CNVA237A2103	CNVA237A2303	CNVA237A2304	CNVA237A2317	CNVA237A2318
Age (years)	60.77 (8.03) [43.10 - 73.01]	63.02 (8.74) [42.39 - 83.64]	67.07 (8.92) [42.93 - 85.75]	63.08 (8.89) [44.28 - 82.54]	64.85 (7.27) [48.66 - 78.21]
Baseline FEV_1 (L)	1.82 (0.64) [0.83 - 3.40]	1.39 (0.51) [0.55 - 3.28]	1.39 (0.46) [0.00 - 2.48]	1.31 (0.49) [0.57 - 2.50]	1.20 (0.47) [0.47 - 2.25]
Body weight (kg)	77.35 (12.22) [50.40 - 105.90]	80.33 (19.82) [46.00 - 154.00]	77.67 (17.60) [42.00 - 128.80]	81.48 (14.49) [52.20 - 115.00]	82.58 (19.36) [46.00 - 129.00]
Glomerular filtration rate ($mL/min/1.73m^2$)	73.25 (10.10) [52.70 - 94.65]	89.24 (20.99) [22.45 - 173.61]	85.84 (19.71) [36.99 - 148.96]	74.62 (15.95) [37.16 - 115.95]	79.61 (18.31) [34.19 - 131.27]

Mean (SD) [Min – Max]. Source: */vob/CNVA237A/pool/pkpd_003/pgm_02//appendix1-tab/Table_5.csv*

(Source: Table 5-3, NVA237 PopPK modeling low dose Report)

Table 10. Summary of categorical covariates by study

Variable	Category	CNVA237 A2103	CNVA237 A2303	CNVA237 A2304	CNVA237 A2317	CNVA237 A2318
Asiatic	No	100.0%	100.0%	83.2%	100.0%	100.0%
Asiatic	Yes	0.0%	0.0%	16.8%	0.0%	0.0%
Ethnicity	Hispanic/Latino	0.0%	2.3%	18.0%	10.9%	0.0%
Ethnicity	Indian (Indian subcontinent)	0.0%	0.0%	0.6%	0.0%	0.0%
Ethnicity	Japanese	0.0%	0.0%	16.2%	0.0%	0.0%
Ethnicity	Mixed Ethnicity	0.0%	3.1%	0.0%	0.0%	12.9%
Ethnicity	Other	100.0%	94.6%	65.3%	65.2%	64.5%
Ethnicity	Unknown or Not Reported	0.0%	0.0%	0.0%	23.9%	22.6%
Japanese	No	100.0%	100.0%	83.8%	100.0%	100.0%
Japanese	Yes	0.0%	0.0%	16.2%	0.0%	0.0%
Known smoker	No	100.0%	47.7%	66.5%	32.6%	41.9%
Known smoker	Yes	0.0%	52.3%	33.5%	67.4%	58.1%
Race	Asian	0.0%	0.0%	16.8%	0.0%	0.0%
Race	Black	0.0%	1.5%	0.0%	8.7%	12.9%
Race	Caucasian	100.0%	97.7%	80.8%	91.3%	83.9%
Race	Native American	0.0%	0.8%	0.0%	0.0%	0.0%
Race	Other	0.0%	0.0%	2.4%	0.0%	3.2%
Sex	Female	42.4%	29.2%	18.0%	39.1%	45.2%
Sex	Male	57.6%	70.8%	82.0%	60.9%	54.8%
Smoking status	Current smoker	0.0%	52.3%	33.5%	67.4%	58.1%
Smoking status	Ex-smoker	0.0%	47.7%	66.5%	32.6%	41.9%
Smoking status	Undefined	100.0%	0.0%	0.0%	0.0%	0.0%

Values are percent of subjects included in the modeling data set. Source: /vob/CNVA237A/pool/pkpd_003/pgm_02//appendix1-tab/Table_3.csv

(Source: Table 5-4, NVA237 PopPK modeling low dose Report)

Population PK Model Development

The population PK model in this report was derived from the existing model by adding a study effect on relative bioavailability to assess potential differences between the phase 3 studies with QD (A2303, A2304) and BID dosing (A2317, A2318).

Structural Model

A three compartment model with first-order absorption (ADVAN12) fitted the glycopyrronium plasma concentrations following NVA237 inhalation. The disposition kinetics was modeled using a parameterization involving apparent total clearance (CL/F), apparent central volume (Vc/F) for the central compartment and apparent inter-compartment clearances (Q3/F and Q4/F), and apparent peripheral volumes (V3/F and V4/F) for the two peripheral compartments (TRANS4). A first-order absorption rate constant (ka) was used to characterize the rapid absorption phase. Between-subject variability in pharmacokinetic parameters (ka, CL/F, Vc/F, Q3/F and V3/F) was modeled using multiplicative exponential model and residual variability was modeled using a proportional error model.

Covariate Model Development

Demographic variables and disease characteristics identified in the previously developed NVA237 population PK model for 50 mcg QD regimen were used as the covariates in the present model. The identified covariates were retested using an automated covariate model building procedure. This process involved a stepwise testing of relationships in a forward inclusion and backward exclusion procedure. The forward inclusion was started with a model including the covariate-relationships identified previously and was performed at a significance level of α=0.01 (ΔOFV of 6.63 for one degree of freedom). The backward exclusion was performed at a significance level of α=0.001 (ΔOFV of 10.83 for one degree of freedom).

Final PK Model Evaluation

Model adequacy was primarily evaluated based on visual inspection of different diagnostic plots and precision of the parameter estimates. The performance of the final model was also evaluated by simulating data using parameter estimates (fixed and random effects) and conducting a visual predictive check (VPC). These diagnostic plots were also stratified by study and occasion to ensure adequacy of the fit across these design factors. Study was selected since it allowed differentiation of regimens (12.5 mcg BID vs 50 mcgQD). Occasion was selected to assess potential changes in the PK profiles over time.

Results

A total of 77 and 330 subjects that inhaled NVA237 BID and QD, respectively were used for model building. Estimated parameters of the final model and alternative model were shown in Table 11 as below.

Final Model: The final model was a three compartment model with first-order absorption. The expressions for typical values (TV) of the parameters were shown as below. Between-subject variability was included for the pharmacokinetic parameters ka, CL/F, Vc/F, Q3/F and V3/F; correlation of the variability of CL/F and Vc/F was estimated. Residual variability was modeled using a proportional error model. Study effects on relative bioavailability were estimated using study A2303 as a reference and there was no significant difference between the two 50 mcg QD studies and the two 12.5 mcg BID studies.

$$TV_F = \theta_{F,study}$$

$$TV_{CL/F} = (\theta_{CL/F} + \theta_{CL\text{-}age} \times (AGE - 60)) \times (BWT/74)^{0.75}$$

$$TV_{Vc/F} = \theta_{Vc/F} \times (BWT/74) \times \theta_{JAP}^{FJAP}$$

$$TV_{Q3/F} = (\theta_{Q3/F} + \theta_{Q3\text{-}age} \times (AGE_i - 60)) \times (BWT/74)^{0.75} \times (\theta_{Q3\text{-}SMH})^{FSM}$$

$$TV_{V3/F} = \theta_{V3/F} \times (BWT/74) \times (\theta_{V3\text{-}SMH})^{FSM}$$

$$TV_{Q4/F} = \theta_{Q4/F} \times (BWT/74)^{0.75}$$

$$TV_{V4/F} = \theta_{V4/F} \times (BWT/74)$$

$$TV_{ka} = \theta_{ka}$$

Alternative Model: The data exploration plots suggested a correlation of eGFR and age (Figure 6). When including eGFR as a potential covariate in the automated search, the search identified that eGFR explains better the observed variability than age: eGFR was selected as a covariate and once eGFR had been included in the model, age was no longer a statistically significant covariate. In the alternative model, CL/F did depend on eGFR and not anymore on age. eGFR was also identified as a covariate on Vc/F and Q3/F. In addition, a dependence of Vc/F on age was identified and of V3/F on smoking status.

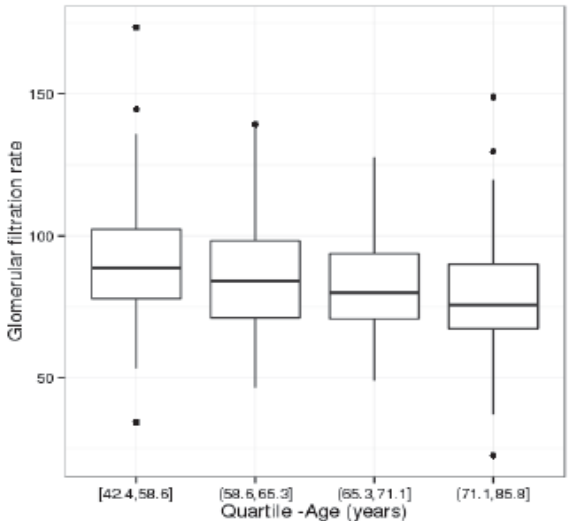


Figure 6. Correlation between age and eGFR
(Source: Adapted from Figure 5-3, NVA237 PopPK modeling low dose Report)

Table 11. NVA237 population PK model parameters

Parameter	Base	Final	All data	Alternative
Objective function	52402.87	52305.89	64874.57	52266.7
Run identifier	run10	run8	run9	run12
CL/F (L/h)	93 (4.3%)	98 (3.8%)	97 (NA)	92 (3.3%)
Vc/F (L)	410 (4.9%)	420 (4.2%)	470 (NA)	380 (4.1%)
Q3/F (L/h)	170 (5%)	180 (6.3%)	160 (NA)	180 (5.9%)
V3/F (L)	2100 (7.1%)	2600 (4.8%)	6300 (NA)	2600 (5.6%)
Q4/F (L/h)	160 (13%)	160 (9%)	200 (NA)	150 (7.4%)

V4/F (L)	110 (12%)	110 (9%)	150 (NA)	100 (7.3%)
ka (1/h)	57 (8.4%)	56 (7.7%)	61 (NA)	56 (7%)
Study effect - 2304 on rel. F	1.1 (5.5%)	1.1 (4.5%)	1.1 (NA)	1.1 (4.1%)
Study effect - 2317 on rel. F	0.92 (6.9%)	0.92 (6.9%)	0.93 (NA)	0.85 (6%)
Study effect - 2318 on rel. F	1.1 (8%)	1.1 (8%)	1.2 (NA)	1.1 (8.3%)
Study effect - 2103 on rel. F	0.79 (8.4%)	0.83 (7.3%)	0.95 (NA)	0.75 (7%)
Residual proportional variability	0.34 (2.6%)	0.34 (2.6%)	0.41 (NA)	0.34 (2.6%)
Residual additive variability	-	-	9.4 (NA)	-
Covariate - weight on CL/F, Q3/F, Q4/F[2)]	0.75 (fixed)	0.75 (fixed)	0.75 (fixed)	0.75 (fixed)
Covariate - weight on Vc/F, V3/F, V4/F[2)]	1 (fixed)	1 (fixed)	1 (fixed)	1 (fixed)
Covariate - age on CL/F	-	-1.1 (20%)	-1.1 (NA)	-
Covariate - age on Q3/F	-	-	-	-
Covariate - Japanese on Vc/F	-	0.75 (11%)	0.73 (NA)	-
Covariate - known smoker on V3/F[1)]	-	0.49 (10%)	0.33 (NA)	-0.53 (8.9%)
Covariate - known smoker on Q3/F	-	0.85 (7.2%)	0.79 (NA)	-
IIV CL/F	0.39 (5%)	0.38 (5.1%)	0.61 (NA)	0.37 (5.6%)
IIV Vc/F	0.57 (4.4%)	0.56 (4.4%)	0.57 (NA)	0.56 (4.4%)
IIV correlation CL/F - Vc/F	0.3 (23%)	0.34 (20%)	0.21 (NA)	0.3 (23%)
IIV V3/F	0.59 (7.3%)	0.45 (14%)	1.5 (NA)	0.47 (12%)
IIV Q3/F	0.59 (4.9%)	0.6 (4.3%)	0.47 (NA)	0.58 (7.3%)
IIV ka	0.99 (6.3%)	0.99 (6.3%)	1 (NA)	0.98 (6.3%)
Covariate - eGFR on CL/F	-	-	-	0.47 (19%)
Covariate - eGFR on Q3/F	-	-	-	0.76 (20%)
Covariate - age on Vc/F	-	-	-	0.014 (24%)
Covariate - eGFR on Vc/F	-	-	-	0.55 (22%)

"Base model" without covariate relationships.
"All data" model, which was identical to the final model but was fitted to all available data including the data points where recording of drug administration or plasma concentration were questionable and had been removed from the primary analysis.
"Alternative" model resulting from the automatic covariate search procedure including eGFR as a potential covariate.
(Source Table 5-5, NVA237 PopPK modeling low dose Report)

Goodness of fit plots for the final model showed an adequate fit of the model with no appreciable systematic trends versus time, time after dose, study, or population prediction suggesting that the final model adequately described the data across these design factors (Figures 7-12).

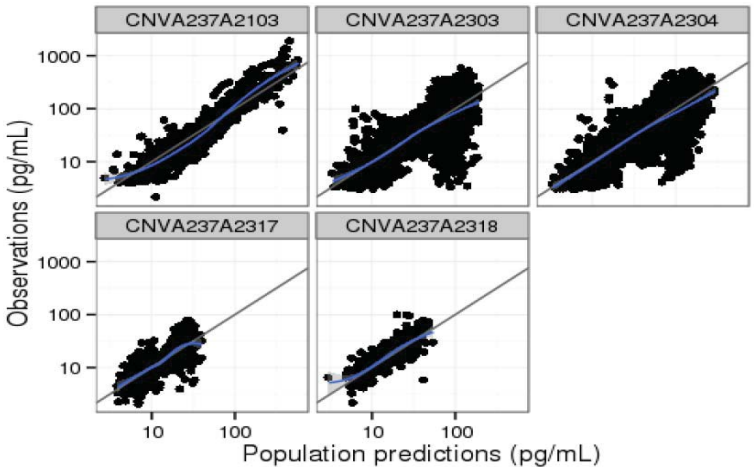


Figure 7. Observed versus population predicted concentration (PRED) by study for the final model
(Source: Figure 5-12, NVA237 PopPK modeling low dose Report)

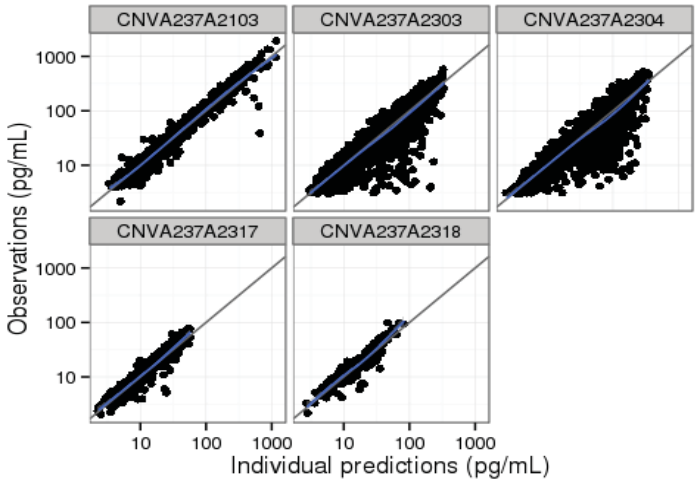


Figure 8. Observed versus individual predicted concentration (IPRED) by study
(Source: Figure 5-13, NVA237 PopPK modeling low dose Report)

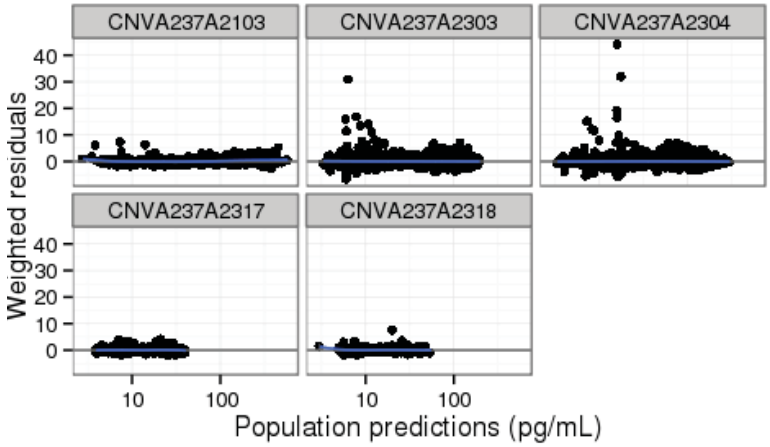


Figure 9. Weighted residuals versus population predicted concentration by study for the final model
(Source: Figure 5-14, NVA237 PopPK modeling low dose Report)

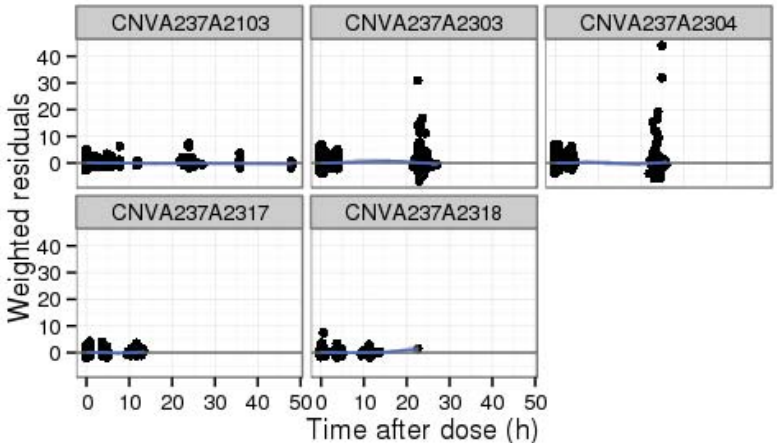


Figure 10. Weighted residuals versus time after dose by study for the final model
(Source: Figure 5-15, NVA237 PopPK modeling low dose Report)

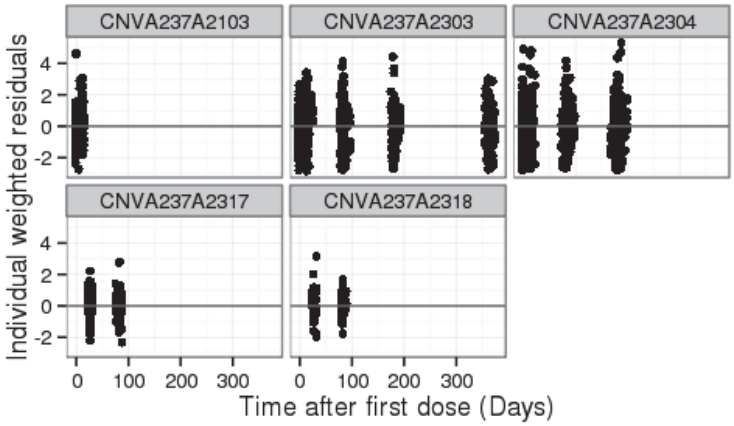


Figure 11. Individual weighted residuals versus time after first dose by study for the final model
(Source: Figure 5-16, NVA237 PopPK modeling low dose Report)

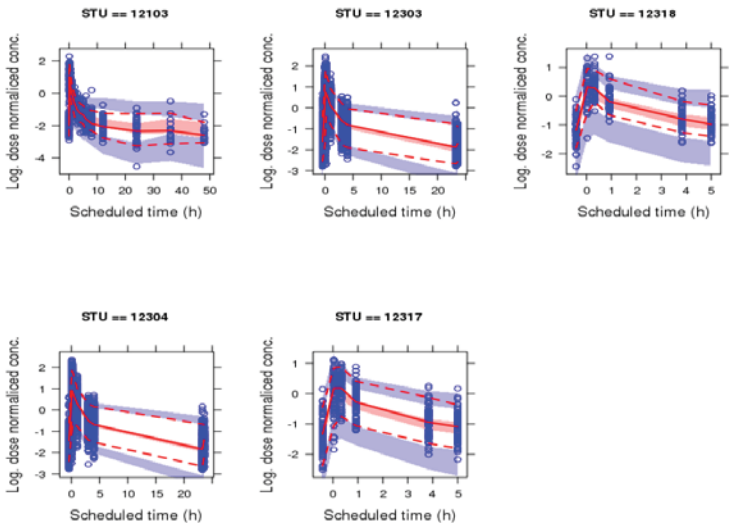


Figure 12. Visual predictive check by study
(Source: Figure 5-17, NVA237 PopPK modeling low dose Report)

Conclusions

- A linear three-compartment PK model with first-order input adequately described the glycopyrronium PK in the COPD patients regardless of regimen, QD or BID.
- Glycopyrronium PK is linear following inhalation of NVA237 12.5 mcg BID or 50 mcg QD.
- NVA237 50 mcg QD regimen resulted in dose proportional two times higher AUC0-24h values than the 12.5 mcg BID regimen.
- Age and body weight were identified as major factors contributing to interpatient variability in CL/F. The dependence of CL/F on age was explained by a decrease in eGFR with age.
- Gender, smoking status, and baseline FEV1 had no apparent effect on maximal or total glycopyrronium systemic exposure following NVA237 inhalation.
- No dependence of CL/F on ethnicity was detected. However peak concentrations were 19% higher in Japanese patients compared to other ethnicities because of a smaller volume of distribution of the central compartment.

Reviewer's comments

The developed population PK model was repeated by the reviewer. The model is adequate to characterize the PK of glycopyrronium following inhalation of NVA237 12.5 mcg BID, and 25, 50, 100, 200 mcg QD and glycopyrronium PK is linear over the tested dose range.

Body weight and eGFR, but not age have been identified as significant covariates contributing to the inter-individual variability in CL/F of glycopyrronium in COPD patients, healthy volunteers, and patients with renal impairment taking NVA237 (see Appendix section 4.1.1) and in COPD patients taking QVA149 (Refer to the Pharmacometrics Review of NDA207930 by Dr. Lei He). In this report, in the final model selected by the sponsor, age and body weight were identified as major factors contributing to interpatient variability in CL/F and the dependence of CL/F on age was explained by a decrease in eGFR with age. However, in the developed alternative model, eGFR was identified to explain the observed variability of CL/F better than age and age was no longer a statistically significant covariate when eGFR was included. In addition, the objective function value of the alternative model is lower than that of the final model, suggesting the alternative model is better than the final model. Therefore, the alternative model with body weight and eGFR as significant covariate on CL/F was believed to better describe glycopyrronium PK in COPD patients, which is also consistent with the previously developed population PK model of glycopyrronium. This is also consistent with the conclusion of "renal elimination is the major elimination pathway of glycopyrrolate" in the Clinical Pharmacology Review.

4.2. Appendix – Individual Study Review

INDIVIDUAL STUDY REVIEW

Note that Studies QVA149A2101, QVA149A2103, QVA149A2105, QVA149A2106, and QVA149A2107 have been submitted and reviewed under NDA207930 (Indacaterol/Glycopyrrolate Inhalation Powder, submitted on 12/29/2014 by Novartis). Refer to the Clinical Pharmacology Review of NDA207930 by Dr. Lei He for further details.

In-Vitro Studies

Summary of studies pertinent to PK using human biomaterials

Table 1. Summary of studies pertinent to PK of NVA237 using human biomaterials

Report	Study Title	Method	Results
DMPK R1200200	In vitro plasma protein binding assessment of NVA237, QBA608, QBA609 and XQA024 in human plasma[a]	Incubation at 37°C for 0.5 h, unbound fraction investigations by ultrafiltration, control experiments were conducted to validate the approach.	The two enantiomers of NVA237, QBA608 and QBA609 showed equivalent plasma protein binding.
DMPK R0600082	In vitro assessment of cytochrome P450 enzyme inhibition by NVA237	Incubations of probe substrates and NVA237 in human liver microsomes.	No significant inhibition of CYP enzymes by NVA237 was observed.
DMPK R0600683	Identification of human enzymes involved in the in vitro metabolism of NVA237	Incubations of [^{14}C]NVA237 in pooled human liver microsomes	Low metabolism was seen with CYP2D6 and only trace metabolism was observed for CYPs 1A2, 2B6, 2C9, 2C18, 2C19, and 3A4. No biotransformation of NVA237 was detected in incubations with other CYPs and FMO1, FMO3, FMO5.
DMPK R0800472	Assessment of efflux transporter (MDR1, MXR, MRP2) inhibition by NVA237	The inhibitory effect of NVA237 on the major efflux transporters from the human ABC family was assessed by determining the compound's ability to inhibit cellular uptake of the probe substrates cyclosporine A (for MDR1), mitoxantrone (for MXR) and valsartan (for MRP2).	No significant inhibition neither of MDR1, MRP2 nor of MXR was observed at NVA237 concentrations up to 300 µM using MDCKII cells as assay system.
DMPK R0800473	Assessment of NVA237 interaction with human OCT1 and OCT2 transporters	The inhibitory effect of NVA237 on the organic anion transporters was assessed by determining the compound's ability to inhibit cellular uptake of the probe substrates [3H]MPP+ (for OCT1), and [14C]metformin (for OCT2).	A significant inhibition of OCT1 and OCT2 was observed using transiently transfected HEK239 cells as assay system. NVA237 was found to be an inhibitor of OCT1 and OCT2 if sufficiently high concentrations are achieved in vivo (i.e. I/IC50≥ 0.1).
DMPK R0800502	Evaluation of NVA237 as an inducer of drug metabolizing enzymes and transporters in human hepatocytes	NVA237 was examined for its potential to induce mRNA and activities of drug-metabolizing enzymes and transporters in cryopreserved human hepatocytes of three individual donors after 48 h of treatment.	At concentrations of up to 50 nM, which exceed > 10-fold clinical concentrations, NVA237 was determined not to be an inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 enzyme activity in hepatocytes. NVA237 did not induce CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9,

			CYP2C19, CYP3A4, CYP3A5, UGT1A1, MDR1, or MRP2 mRNA.
DMPK R0800758	Uptake transporter (OCT1, OCT2) phenotyping for NVA237	The potential of NVA237 to inhibit human OCT1 and OCT2 activity was assessed using HEK293 cells transiently transfected with OCT1 or OCT2. Selective inhibitors such as decynium-22 and phenoxybenzamine were used to inhibit uptake of NVA237.	NVA237 was identified as a substrate for OCT1 and OCT2 with a Km of 125 μM and 119 μM respectively. If sufficient high plasma concentrations of NVA237 are reached, interactions with other drugs that are substrates or inhibitors of OCT1 or OCT2 might lead to a reduced elimination of NVA237.
DMPK R0900807	Assessment of NVA237 as a substrate of the human multidrug and toxin extrusion transporters, MATE1 and MATE2K	The uptake of [14C]NVA237 into HEK Flp-In cells (passage 16) and HEK Flp-In cells stably expressing hMATE1 (passage 12) or hMATE2K (passage 12) was conducted to determine if NVA237 was a substrate of either transport protein.	[14C]NVA237 was found to be transported by hMATE1, but not hMATE2K, in HEK Flp-In cells stably expressing the respective transport proteins. MATE1 likely acts in concert with OCT2 to accomplish renal tubular secretion of NVA237 in humans. Inhibition of either OCT2 or MATE1 may affect the renal excretion of NVA237 and its PK.
DMPK R1000619	In vitro assessment of cytochrome P450 2B6 inhibition by NVA237	The potential of NVA237 to inhibit human CYP enzyme activity was assessed in pooled human liver microsomes by testing the effect of increasing concentrations of NVA237 on the in vitro metabolism of a CYP2B6-selective probe substrates.	NVA237 is not expected to inhibit the metabolic clearance of co-medications metabolized by human CYP2B6.
DMPK R1100757	Assessment of hydrolytic enzymes involved in the in vitro human metabolism of NVA237	Incubation of [14C]NVA237 with HIS9, HLS9, human purified recombinant enzymes and human plasma	Enzymatic hydrolysis was not observed in pooled human intestine and liver S9 fractions. M9 formation was catalyzed by human butyrylcholinesterase (BChE) and, to a lesser extent, by human acetylcholinesterase (AChE). Human recombinant carboxylesterases (CEs) did not catalyze the formation of M9.
DMPK R1200048	Assessment of uptake transporter (OAT1, OAT3) inhibition by NVA237	The inhibitory effect of NVA237 up to 200 μM on the major OAT uptake transporters was assessed by determining the compound's ability to inhibit cellular uptake of the probe substrate [3H]p-Aminohippuric acid for OAT1 and of [3H]Estrone-3-sulfate for OAT3, respectively.	NVA237 was not found to be an inhibitor of OAT1 abd OAT3 up to the highest concentration investigated (200 μM).
DMPK R1200049	Assessment of uptake transporter (OATP1B1, OATP1B3) inhibition by NVA237	The inhibitory effect of NVA237 up to 200 μM on the major uptake Transporters, OATP1B1 and OATP1B3, was assessed by determining the compound's ability to inhibit cellular uptake of the probe substrate estradiol-17β-D-glucuronide (E17G) for OATP1B1 and OATP1B3.	NVA237 was not found to be an inhibitor of OATP1B1 or of OATP1B3 up to the highest concentration investigated (200 μM).
DMPK R0800705	Uptake of NVA237 into human hepatocytes	Hepatic uptake was assessed by measuring the time-, temperature- and concentration-dependant	Human hepatocyte uptake of NVA237 occurs, most likely, solely by a slow passive permeation

		NVA237 uptake. The involvement of several candidate transporter families (OAT, OATP, OCT) was investigated using representative uptake transporter inhibitors.	process. Hepatic uptake was in a low range with human hepatic clearance (CLm) around 7 µL/min/mg.
DMPK R1000635	Assessment of the intestinal transport of NVA237 using the gastrointestinal Caco-2 cell line	Transport in apical-to-basolateral (AP-BL) and basolateral-to-apical (BL-AP) direction was determined in the presence and absence of well-known efflux pump inhibitors. Additionally, formation of the NVA237 metabolite CJL603 was measured.	NVA237 has a low passive permeability across Caco-2 cell monolayers. No modulation of NVA237 transport by drug transporters was identified. In addition, no substantial conversion of NVA237 to CJL603 (M9) was found.

a. NVA237 is a racemic mixture of the two enantiomers QBA608 and QBA609. XQA024 is a compound currently marketed for the treatment of COPD.

PK Study in COPD Patient

Study NVA237A2103

Title: A multi-center, randomized, double-blind, parallel-group study to investigate the pharmacokinetics, pharmacodynamics, safety and tolerability of multiple inhaled NVA237 doses at four dose levels in COPD patients.

Objectives

Primary: to assess the PK of NVA237 following single and repeated once-daily inhaled NVA237 doses in COPD patients.

Secondary:

- To evaluate the PD and the PK/PD relationships of NVA237 following single and repeated once-daily inhaled NVA237 doses in COPD patients
- To evaluate the safety and tolerability

Study Design and Treatment Schedule:

This was a multi-center, randomized, double-blind, parallel-grouped design study in COPD patients. A total of 40 mild to moderate COPD patients were to be randomized to one of five treatments (placebo, NVA237 25, 50, 100, 200 mcg). Study medication was taken QD via the Concept1 device for 2 weeks. After patients received their first dose of study medication on Day 1and 14, they remained at the study site up to 24 hours to complete spirometric, pharmacokinetic and safety assessments.

Table 2 Tested Product

Treatment	Device	Batch #
NVA237 25 mcg, QD, 14 days	Concept 1	X010 0107
NVA237 50 mcg, QD, 14 days	Concept 1	X008 0107
NVA237 100 mcg, QD, 14 days	Concept 1	X011 0107
NVA237 200 mcg, QD, 14 days	Concept 1	X012 0107
Placebo, QD, 14 days	Concept 1	X016 0107

PD Assessment

Spirometry (FEV_1 and FVC) was the only type of pharmacodynamic assessment. Spirometry was assessed in screening visit, baseline, Day 1 and Day 14.

PK Sampling Schedule

Blood samples

PK profile samples were taken on Days 1 and 14 at the following time points: pre-dose, 5, 15, 30 minutes, and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose. Additional samples were collected at 36 and 48 hours post-dose on Day 14. Trough PK samples were collected on Days 2, 5, 7 and 9 prior to drug inhalation.

Urine samples

On Days 1 and 14, urine was collected during the following intervals: 0-4h, 4-8h and 8-24h after dosing.

Analysis of NVA237 in plasma and urine was performed by a validated LC-MS/MS method with a LLOQ of 4 pg/mL in plasma and 20 pg/mL in urine.

Results

PD results

The statistical analysis of change from baseline for E_{max} and trough FEV_1 was shown in the Table 3. E_{max} increased compared to placebo for all doses on both Day 1 and Day 14 but most notably for the NVA237 50 and 200 mcg doses on Day 1 with means of 295 mL and 298 mL (P=0.009 and 0.005 respectively). There was a numerical improvement in all treatment groups in trough FEV_1 with the exception of NVA237 200 mcg on Day 14 and NVA237 25 mcg on Day 1.

The dose-response relationship of Emax FEV1 change from baseline on Day 1 and Day 14 and indicates that there is greater variability of individual points in the 50 mcg dose on both days that is impacting the dose response.

Table 3. Summary of the statistical analysis of change from baseline in FEV1 on Days 1 and 14

Variable	Day	Treatment	LS mean (90% CI)	Contrast to Placebo LS mean (90% CI)	P-value
E_{max} FEV_1 (L)	1	Placebo	0.217 (0.093, 0.341)		
		NVA237 25 µg	0.324 (0.203, 0.446)	0.107 (-0.067,0.281)	0.31
		NVA237 50 µg	0.512 (0.381, 0.643)	0.295 (0.112, 0.478)	0.009
		NVA237 100 µg	0.414 (0.292, 0.535)	0.197 (0.023, 0.370)	0.063
		NVA237 200 µg	0.515 (0.400, 0.630)	0.298 (0.127, 0.469)	0.005
	14	Placebo	0.208 (0.084, 0.332)		
		NVA237 25 µg	0.347 (0.226, 0.469)	0.139 (-0.035,0.313)	0.19
		NVA237 50 µg	0.391 (0.260, 0.523)	0.183 (0.000, 0.366)	0.099
		NVA237 100 µg	0.346 (0.225, 0.468)	0.138 (-0.035, 0.312)	0.19
		NVA237 200 µg	0.399 (0.280, 0.517)	0.190 (0.017, 0.363)	0.071
Trough FEV_1 (L)*	1	Placebo	0.023 (-0.096,0.142)		
		NVA237 25 µg	-0.023 (-0.140,0.093)	-0.046 (-0.213,0.120)	0.64
		NVA237 50 µg	0.208 (0.083,0.333)	0.185 (0.010,0.360)	0.082
		NVA237 100 µg	0.195 (0.079,0.311)	0.172 (0.006,0.338)	0.089
		NVA237 200 µg	0.159 (0.049,0.269)	0.136 (-0.027,0.300)	0.17
	14	Placebo	-0.031 (-0.150,0.088)		
		NVA237 25 µg	0.025 (-0.091,0.141)	0.056 (-0.110,0.222)	0.57
		NVA237 50 µg	0.116 (-0.009,0.242)	0.147 (-0.028,0.322)	0.16
		NVA237 100 µg	0.138 (0.022,0.255)	0.169 (0.003,0.336)	0.093
		NVA237 200 µg	-0.057 (-0.170,0.055)	-0.026 (-0.191,0.139)	0.79

* Calculated as $AUE_{23\text{-}24h}$

(Source: Table 11-2, Study NVA237A2103 report)

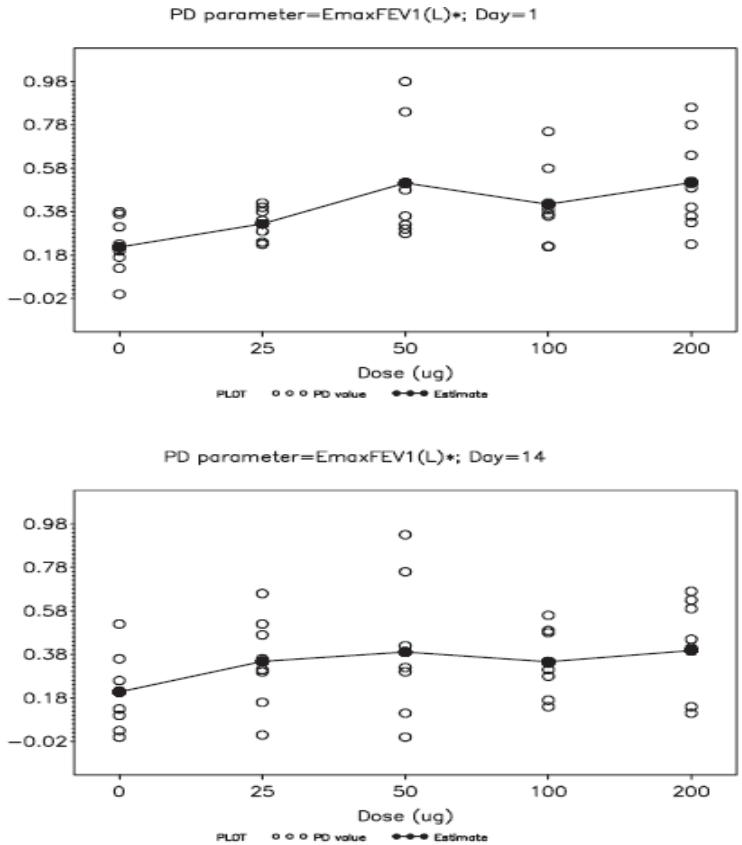


Figure 1. Dose-Response Relationship of Emax FEV1 change from baseline on Day 1 and Day 14

(Source: Figure 11-1, Study NVA237A2103 report)

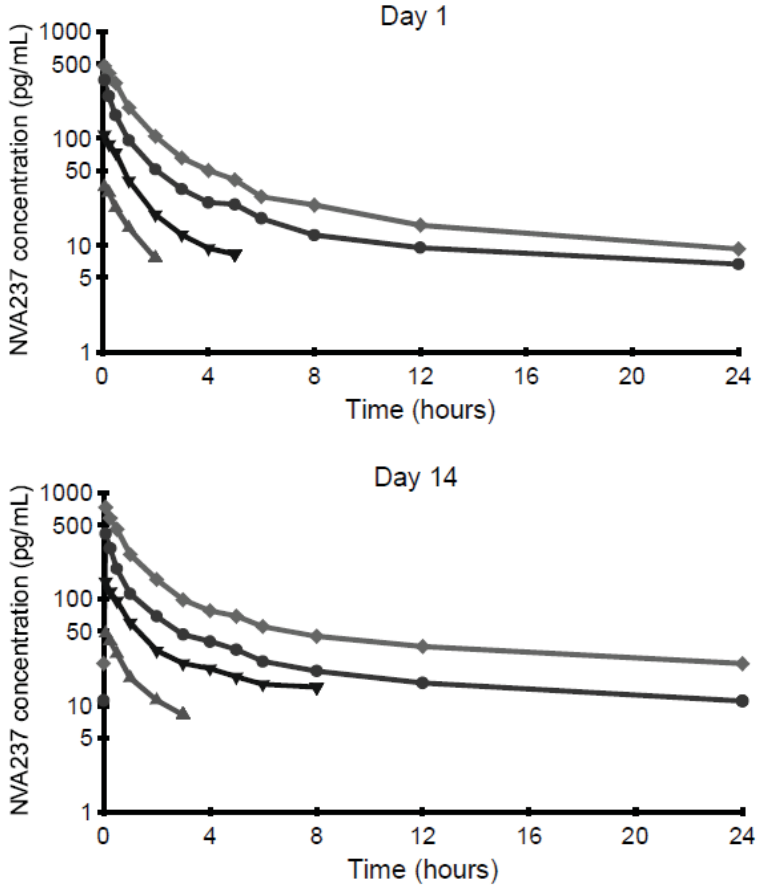
PK results

Plasma PK

The mean plasma concentration-time profiles and mean trough plasma concentrations of glycopyrronium for each treatment of NVA237 were shown in the following Figures 2 and 3. The key plasma PK parameters of NVA237 after single daily inhaled doses of NVA237 in each treatment group on Days 1 and 14 are summarized in Table 4.

NVA237 was systemically available shortly after inhalation (mean Tmax is ~5 or 6.5 min) and plasma concentrations decreased rapidly thereafter. Following Tmax, plasma concentration of NVA237 fell rapidly. It should be noted that the plasma concentration-time profiles for the 25 mcg dose on Days 1 and 14 as well as for the 50 mcg dose on Day 1 were truncated due to the limited assay sensitivity.

The trough levels indicate that steady-state was achieved by Day 7. Results from Day 1 and Day 14 indicated a linear dose response over 50 to 200 mcg (100 to 200 mcg for AUC_{0-24} on Day 1), with both AUC_{0-24} and C_{max} approximately doubling with doubling of the dose. The ratios of Day 14 to Day 1 indicated some accumulation of the drug and the extent of accumulation tended to increase with increasing dose. The accumulation at the 100 and 200-mcg doses had 90% CI being above 1.0 (Table 5).



NVA237 Doses: ▲= 25 µg; ▼= 50 µg, ● = 100 µg, ♦= 200 µg

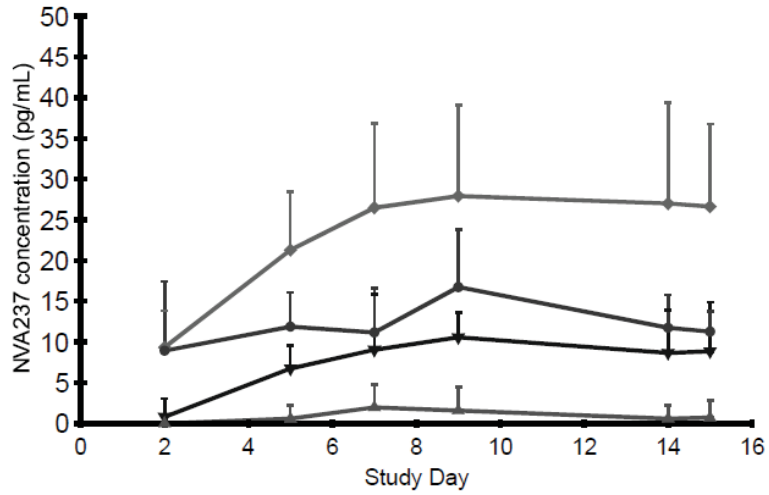
Note: for clarity the x axis is shown only up to 24 hours postdose on Day 14

Figure 2 Geometric mean plasma concentration-time profiles of NVA237 for each NVA237 dose on Day 1 and Day 14
(Source: Figure 11-2, Study NVA237A2103 report)

Table 4. Summary statistics of key NVA237 plasma pharmacokinetic parameters

Dose [µg] (n)	t_{max} [a] [h]	C_{max} [pg/mL]	$C_{min,ss}$ [pg/mL]	C_{avg} [pg/mL]	AUC_{0-24} [pg*h/mL]	CL/F [L/h]	$t_{1/2}$ [h]	PTF [%]	R_{acc}	$t_{1/2,acc}$ [h]
Day 1										
25 (8)	0.08 (0.08-0.25)	41 (20.8)	-	-	n.d.	n.d.	n.d.	-	-	-
50 (7)	0.08 (0.08-0.50)	146 (109)	-	-	n.d	n.d.	n.d	-	-	-
100 (8)	0.08 (0.08-0.12)	360 (79.6)	-	-	568 (146)	162 [b] (32.8)	13.71 [b] (2.46)	-	-	-
200 (9)	0.08 (0.07-0.50)	565 (248)	-	-	1028 (320)	176 [b] (75.6)	13.03 [b] (9.30)	-	-	-
Day 14										
25 (8)	0.11 (0.08-0.25)	51 (17.4)	0.6 (1.66)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
50 (8)	0.08 (0.08-0.25)	166 (97.3)	8.2 (5.14)	19.3 (8.87)	464 (213)	132 (66.7)	13.43 [c] (8.02)	870 (396)	n.d.	n.d.
100 (8)	0.08 (0.08-0.25)	436 (135)	10.6 (2.66)	32.4 (6.45)	778 (155)	133 (27.4)	20.77 [d] (8.61)	1294 (231)	1.45 (0.45)	16.10 [b] (6.29)
200 (8)	0.08 (0.08-0.10)	865 (545)	25.3 (9.65)	74.2 (27.21)	1780 (653)	133 (71.5)	21.64 [c] (3.24)	1070 (397)	1.90 (0.77)	21.87 (13.35)

n.d.= not determined.
[a] median (min-max); [b] n=7; [c] n=4; [d] n=3
(Source: Table 11-3, Study NVA237A2103 report)



NVA237 Doses: ▲= 25 µg; ▼= 50 µg, ● = 100 µg, ♦= 200 µg
Note: The Day 15 values are the 24-hour postdose concentrations on Day 14

Figure 3 Arithmetic mean (plus SD) trough plasma concentration of NVA237 for each NVA237 dose
(Source: Figure 11-3, Study NVA237A2103 report)

Table 5. Statistical results for PK parameters of NVA237

PK parameter (unit)	Treatment	Least squares mean and 90% CI		
		Day 1	Day 14	Ratio Day 14/Day 1
AUC_{0-24} (h.pg/mL)	50 µg	-	407 (335, 495)	-
	100 µg	569 (461, 702)	817 (722, 925)	1.44 (1.15, 1.79)
	200 µg	970 (793, 1186)	1641 (1349, 1995)	1.69 (1.34, 2.13)
C_{max} (pg/mL)	50 µg	129 (96, 174)	158 (118, 210)	1.22 (0.94, 1.58)
	100 µg	273 (227, 327)	355 (297, 426)	1.30 (1.11, 1.53)
	200 µg	575 (437, 758)	802 (605, 1064)	1.39 (1.09, 1.78)

- AUC_{0-24} not determined on Day 1

(Source: Table 11-7, Study NVA237A2103 report)

Urine PK

The summary of key urine PK parameters is presented in Table 6. Mean Ae_{0-24} increased over the dose range of 25 to 200 mcg by a factor of 11.7 on Day 1 and 10.3 on Day 14. The fraction of the NVA237 dose recovered in urine ranged from 6.7 to 9.8% on Day 1 and from 11.6 to 15.0% on Day 14. Renal clearance (CL_R), which was determined for the 100 and 200 mcg doses on Day 1 and for the 50, 100 and 200 mcg-doses on Day 14, was similar on both Days 1 and 14 and across the dose groups.

Table 6. Summary statistics of key NVA237 urine PK parameters

Dose [µg] (n)	Ae_{0-24} [µg]	Ae_{0-24} [%]	CL_R [L/hr]
Day 1			
25 (7)[1]	1.67 (0.60)	6.68 (2.40)	n.a.
50 (7)	3.87 (1.45)	7.74 (2.90)	n.a.
100 (7)[1]	9.80 (2.52)	9.80 (2.52)	17.4 (4.62)
200 (8)[1]	19.6 (4.39)	9.81 (2.19)	20.6 (3.88)
Day 14			
25 (8)	2.90 (1.10)	11.6 (4.42)	n.a.
50 (8)	7.21 (1.68)	14.4 (3.36)	17.6 (6.40)
100 (8)	14.1 (5.04)	14.1 (5.04)	18.6 (6.20)
200 (8)[1]	30.0 (10.8)	15.0 (5.38)	17.4 (4.57)

[1] PK urine collection not complete or available in n=1 subject of the dose group

(Source: Table 11-4, Study NVA237A2103 report)

Conclusions

- NVA237 was systemically available shortly after inhalation (Tmax ~5-6.5 mins) in all dose groups on both Days 1 and 14.
- At steady-state, systemic exposure (AUC_{0-24}, C_{max}) to glycopyrronium and amount excreted into urine (Ae_{0-24}) increased about dose-proportionally within 50-200 mcg dose.

- Following multiple NVA237 QD inhalation, steady-state was reached within one week. The accumulation ratios for glycopyrronium AUC (Day 14/Day 1) were 1.44 and 1.69 for the 100 and 200 mcg, respectively.
- The mean apparent T1/2 of glycopyrronium determined for the 50 mcg (Day 14 only), 100 mcg and 200 mcg doses ranged between 13 and 22 hours. The mean effective half-life ($t_{1/2,acc}$) determined from the AUC accumulation ratios for the 100 mcg and 200 mcg doses was 16 and 22 h, respectively.
- 6.7 -9.8% (on Day 1) and 11.6 -15.0% (on Day 14) of the NVA237 dose were recovered as unchanged drug in urine over the 25-200 mcg doses.
- Renal clearance (CL_R) of NVA237 was similar across the dose groups (50-200 mcg) and after single and repeated dosing.
- The urinary elimination of the NVA237 enantiomers, QBA608 and QBA609, was similar.
- At steady state (Day 14), on average about 3% of the dose were recovered in urine as glucuronide and/or sulfate conjugates of NVA237.
- There was no PK/PD correlation between the NVA237 systemic exposure after inhalation and the drug response (FEV_1 and FVC).
- The investigated doses of NVA237 were safe and well tolerated.

Intrinsic Factor

Study NVA237A2104

Title: An ethnic sensitivity study to assess the pharmacokinetics, safety, and tolerability of NVA237 in Caucasian and Japanese healthy male subjects administered at three dose levels using a randomized, double-blind, crossover design within each ethnic group

Objectives:

Primary

- To assess the NVA237 PK including dose proportionality following single inhalation of NVA237 in Caucasian and Japanese healthy male subjects
- To evaluate ethnic differences in the NVA237 PK between Caucasian and Japanese healthy male subjects

Secondary

- Safety and tolerability

Study Design and Treatment Schedule:

This was a randomized, double-blind, crossover design with planned enrollment of 36 healthy male subjects of two ethnic origins (18 Japanese and 18 Caucasians). Subjects received single inhaled doses of NVA237 (50, 100, and 200 mcg), with a washout period of at least 7 days (and no more than 14 days) between doses. There were six treatment sequences each with three subjects in both ethnic groups. The study consisted of a 21-day Screening period, three baseline periods (Day –1) (one before each treatment period), and three treatment periods (Day 1), followed by a Study Completion evaluation performed 2 to 14 days after the last drug administration.

Table 7. Test drug product

Treatment	Device	Batch #
NVA237 single inhalation 50mcg	Concept 1	X008 0107
NVA237 single inhalation 100mcg	Concept 1	X011 0107
NVA237 single inhalation 200mcg	Concept 1	X0120107

PK Sampling Schedule

Blood samples

Blood samples were collected on treatment period Days 1, 2, and 3 at predose, 0.083, 0.167, 0.25, 0.5, 1, 1.5, 2, 4, 5, 6, 8, 12, 24, 36, and 48 hours postdose.

Urine samples

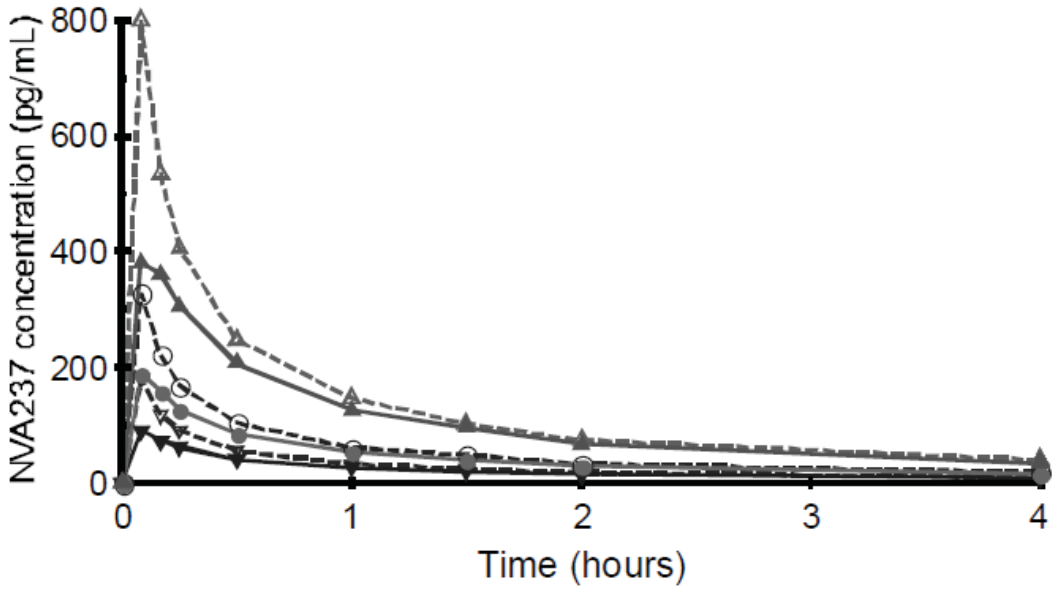
Urine samples were collected from each subject before drug administration (pre-dose) and during the following collection intervals: 0-4, 4-8, 8- 24, and 24-48 hours postdose.

Results

Following NVA237 inhalation, median Tmax in both ethnic groups for different doses was 5 min. Cmax, AUC0-24 and AUC0-tlast were higher in Japanese subjects than in Caucasians at all dose levels. The statistical analysis of plasma PK parameters showed dose proportionality of Cmax over the studied dose range (50 to 200 mcg) for both the Japanese and Caucasian cohorts, but not for AUC0-t and AUC0-24. AUC0-24 can be considered proportional to the increase in dose within a dose range characterized by a dose multiple of 3.0 (Caucasian) and 3.8 (Japanese) (Figure 4 and Table 8, 9).

The mean amount of NVA237 excreted into urine within 48 h after inhalation amounted to 9.5-10.2% of the dose in Caucasian subjects and to 13.0-15.5% of the dose in Japanese subjects. The CLr, which was determined for the 100 and 200 mcg doses, was similar for both ethnic groups and doses ranging19.8 -24.4 L/hr on average. The Ae0-48 ratio was between 1.38 and 1.46. The CLr ratio was 0.97 and 1.11 for the 100 and 200 mcg doses respectively (Figure 5 and Table 8, 10).

It should be noted that, due to the limited assay sensitivity (LLOQ of 4 pg/mL in plasma and 20 pg/mL in urine), after the 50 mcg dose, the last measurable concentration of NVA237 in the individual subjects was found between 4 and 48 hours and the NVA237 concentration-time profiles were truncated in 11 and 5 Caucasian and Japanese healthy volunteers, respectively, at or before 8 hours postdose because the plasma concentrations were below the LLOQ at latter time points. Renal clearance was not calculated for the 50 mcg dose for the same reason.

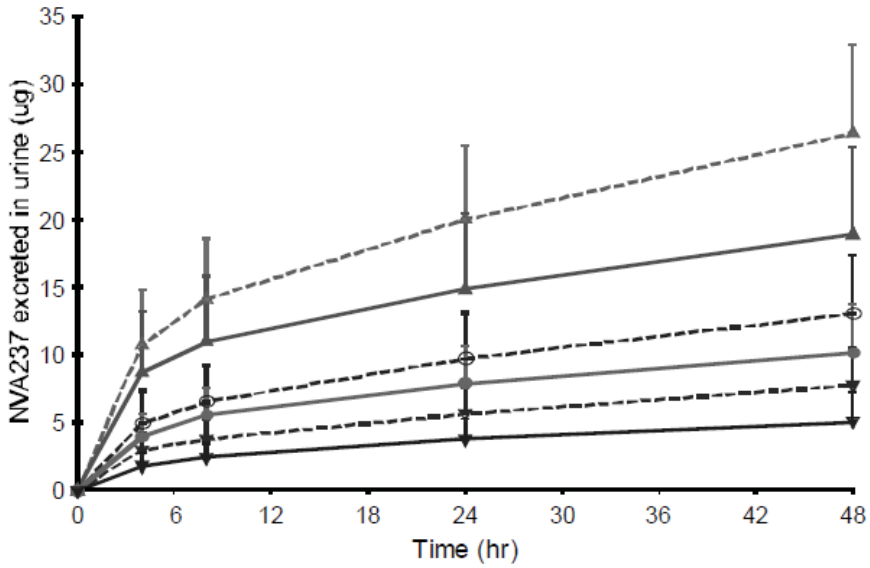


Note: for clarity the x axis is shown only up to 4 hours postdose

NVA237 doses in Caucasian (—; closed symbols) and Japanese (---; open symbols) healthy volunteers: ▼ / ▽ = 50 µg; ● / ○ = 100 µg, ▲ / △ 200 µg

Figure 4. Mean plasma concentration-time profiles of NVA237 for each dose per ethnic group

(Source: Figure 1-1, Study NVA237A2104 report)



NVA237 Doses in Caucasian (—; closed symbols) and Japanese (---; open symbols) healthy volunteers: ▼/ ▽ = 50 µg; ● / ○= 100 µg, ▲ / △ 200 µg

Figure 5, Mean (+SD) cumulative urine excretion of NVA237 per dose and ethnic group

(Source: Figure 1-2, Study NVA237A2104 report)

Table 8. Key plasma and urine PK parameters after single inhaled doses of NVA237 in each ethnic group (means ± SD)

Parameter	Caucasian			Japanese		
	NVA237 50 µg N=19	NVA237 100 µg N=17	NVA237 200 µg N=18	NVA237 50 µg N=17	NVA237 100 µg N=18	NVA237 200 µg N=18
t_{max} [a] [h]	0.08 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.25)	0.08 (0.08-0.08)	0.08 (0.02-0.15)	0.08 (0.08-0.17)
C_{max} [pg/mL]	94 (± 35.7)	192 (± 97.2)	401 (± 129)	181 (± 95.6)	328 (± 142)	801 (± 359)
$AUC_{0-tlast}$ [pg*h/mL]	164 (± 122)	416 (± 181)	968 (± 231)	257 (±154)	578 (± 219)	1269 (± 357)
AUC_{0-24} [pg*h/mL]	147 (± 77.5)	330 (± 115)	746 (± 175)	209 (±106)	421 (± 147)	930 (± 287)
Ae_{0-48} [µg]	5.10 (± 2.17)	10.15 (± 3.55)	18.89 (± 6.46)	7.77 (± 2.61)	13.04 (± 4.28)	26.34 (± 6.52)
Ae_{0-48} [% dose]	10.2 (± 4.34)	10.2 (± 3.55)	9.45 (± 3.23)	15.5 (± 5.23)	13.0 (± 4.28)	13.2 (± 3.26)
CL_R [L/hr]	n.d.	24.4 (± 5.00)	19.8 (± 5.38)	n.d.	23.5 (± 4.89)	21.4 (± 4.47)

n.d.= not determined; [a] median (min-max)
Source: Post-text Table 14.2-1.2, Post-text Table 14.2-1.3, Post-text Table 14.2-1.5
(Source: Table 11-3, Study NVA237A2104 report)

Table 9. Estimate of the geometric mean ratios (Japanese/Caucasian) for plasma PK parameters at each dose level

PK parameter (unit)	Dose (µg)	Estimated ratio of geometric means	Lower 90% confidence limit	Upper 90% confidence limit
$AUC_{0-tlast}$ (pg*h/mL)	50	1.49	1.15	1.93
	100	1.40	1.12	1.74
	200	1.31	1.02	1.70
AUC_{0-24} (pg*h/mL)	50	1.34	1.078	1.663
	100	1.28	1.058	1.555
	200	1.23	0.989	1.527
C_{max} (pg/mL)	50	1.76	1.38	2.25
	100	1.80	1.45	2.24
	200	1.84	1.44	2.35

Source: Post-text Table 14.2-1.10
(Source: Table 11-4, Study NVA237A2104 report)

Table 10. Estimate of the geometric mean ratios (Japanese/Caucasian) for urine PK parameters at each dose level

PK parameter (unit)	Dose (µg)	Estimated ratio of geometric means	Lower 90% confidence limit	Upper 90% confidence limit
Ae_{0-48} (pg)	50	1.46	1.22	1.74
	100	1.42	1.21	1.66
	200	1.38	1.15	1.65
CL_R	100	0.97	0.847	1.114
	200	1.11	0.967	1.268

Source: Post-text Table 14.2-1.10; CL_R was not determined for the 50 µg dose
(Source: Table 11-5, Study NVA237A2104 report)

Conclusions

- Tmax was 5 minutes after NVA237 inhalation in both ethnic groups at all dose levels.
- Systemic exposure (Cmax, AUC0-tlast) and urinary excretion of NVA237 (Ae0-48) were on average 30%- 80% higher in Japanese than in Caucasian subjects.
- The renal clearance (CLr) of NVA237 was similar in both ethnic groups, suggesting there is no ethnic difference in the main elimination pathway of NVA237.
- Cmax and Ae0-48 of NVA237 showed dose proportionality across the 50 to 200 mcg dose range for both Japanese and Caucasian subjects. Mean AUC0-tlast increased about 6-fold (Caucasians) and 5-fold (Japanese) across 50 to 200 mcg dose range.

Intrinsic Factor

Study CNVA237A2105

Title: An open label, non-randomized, parallel-group study to characterize and compare the pharmacokinetics, safety, and tolerability of a single dose of NVA237 in subjects with mild, moderate, severe and end-stage renal impairment with that in matched healthy control subjects.

Objectives

Primary: to determine the NVA237 PK in subjects with mild, moderate, severe or end-stage renal impairment following the inhalation of 100 mcg NVA237.

Secondary:

- to measure the effect of (hemo) dialysis on the PK of NVA237 in subjects with end-stage renal disease requiring dialysis
- to evaluate the safety and tolerability

Study Design and Treatment Schedule:
This was a single-dose, open-label, non-randomized, parallel-group study in subjects with mild, moderate, severe or end-stage renal impairment and healthy volunteers. Each renally impaired subject was appropriately matched to a healthy volunteer. The study consisted of a 28-day screening period, a baseline period, one treatment period followed by an end of study evaluation.

In Period 1, eight subjects were recruited into each group according to their degree of renal impairment. For ESRD subjects, no dialysis was performed from the time of drug administration on Day 1 up to 72 hours post-dose in Period 1. A control group of appropriately matching HVs (in terms of weight, age and gender) was recruited.

In Period 2, the effect of dialysis on the NVA237 PK in the ESRD subjects was evaluated following a washout of at least three weeks. Following the oral inhalation of a dose of

100 mcg NVA237 on Day 1, subjects remained domiciled for at least 72 hours for collection of blood and dialysate for PK and safety assessments (Tables 11-13).

Table 11. Study design schema

Study Phase		Period 1		Wash-out		Period 2 ESRD subjects only	
Day -30 to -2	Day-1	Day 1 to Day 4	Day 5	≥ 3 weeks	Day-1	Day 1 to Day 3	Day 4
Screening	Base-line	Treatment period (up to Day 3 for ESRD subjects)	End of Study except for ESRD subjects	ESRD subjects only	Base-line	Treatment period (with 4-hour dialysis from drug administration)	End of Study for ESRD subjects

(Source: Table 9-1, Study NVA237A2105 report)

Table 12. Test Product

Treatment	Device	Strength	Batch #
NVA237 single inhalation 100mcg	Concept 1	50mcg capsules	X144GF
Matching placebo	Concept 1	placebo capsules	X137EF

Table 13. Treatment groups

Group 1 (n = 8-32)*	Healthy volunteers control group receiving 100 µg (eGFR >80 mL/min/1.73m^2)
Group 2 (n = 8)	Mild renal impairment (eGFR 50-80 mL/min/1.73m^2) receiving 100 µg NVA237
Group 3 (n = 8)	Moderate renal impairment (eGFR 30-49 mL/min/1.73m^2) receiving 100 µg NVA237
Group 4 (n = 8)**	Severe renal impairment (eGFR <30 mL/min1.73m^2) receiving 100 µg NVA237.
Group 5 (n = 8)**	End-stage subjects requiring dialysis (ESRD) receiving 100 µg NVA237

Notes: *The number of healthy volunteers was determined by the number needed to find a corresponding match for each renally impaired patient. The allowed number of healthy volunteers to be recruited was between 8 and 32; actually 18 healthy subjects were recruited.
**If the recruitment of n=8 subject was not possible in the selected center, less subjects might have been enrolled; actually 6 ESRD subjects were recruited.
(Source: Table 9-3, Study NVA237A2105 report)

PK Sampling Schedule

Blood samples
For Period 1 (all subjects): PK samples (5mL) were collected pre-dose (0) and at 0.08, 0.17, 0.25, 0.5, 1, 1.5, 2, 4, 5, 6, 8, 12, 14, 26, 48, 72 and 96 hours post dose (the 96-h PK sample was not collected in the ESRD subjects).

For Period 2 (ESRD subjects only): During dialysis (from 0 to 4 hours), pairwise 5mL blood samples were taken from the inflow and outflow tracts at 0.08, 0.17, 0.25, 0.5, 1, 1.5, 2 and 4 hours post dose. Following dialysis (from 5 to 72 hours) blood samples were taken as for Period 1.

Urine samples
For Period 1 (all subjects): pre-dose, 0-4, 4-8, 8-24, 24-48, 48-72 and 72-96 hours post dose (no urine collection was performed in the ESRD subjects), 6ml aliquots taken from pooled samples.

Results

Plasma PK results

The NVA237 concentration-time profiles, PK parameters in Period 1, and statistical analysis are shown in Figure 6, Table 14 and Table 15. Results indicate the median Cmax was reached at 5 minutes after inhalation for all groups except the ESRD group where it occurred at 7.5 minutes post inhalation. The mean T1/2 was apparently longer for all the renally impaired groups than for the healthy volunteers. The longest T1/2 was observed in the ESRD group (i.e. 61.7 hr), which was almost twice longer than the T1/2 observed in the HV group. In statistical sensitivity analysis (each RI group was compared jointly to all 18 HVs, however still maintaining the pair information), compared with healthy volunteers, AUClast in the mild group increase 42% whilst the moderate group had a similar AUClast. For the severe and ESRD groups, the AUClast were 2.21- and 2.07-fold of that in HVs, respectively. However, the Cmax remain similar or slightly lower in RI subjects compared to HVs.

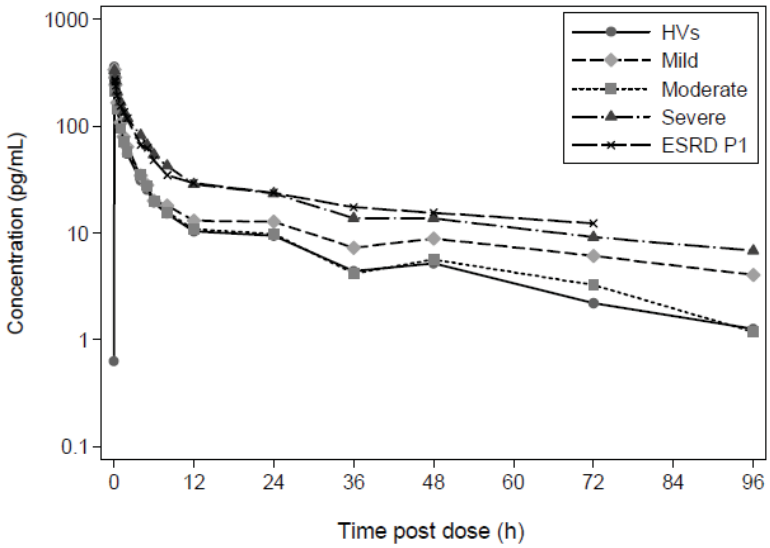


Figure 6. Arithmetic mean NVA237 plasma concentration time-profiles (Period 1)
(Source: Figure 11-1, Study NVA237A2105 report)

Table 14. Summary of key plasma PK parameters (PK analysis set, Period 1)

PK parameter		Renally impaired subjects				Healthy volunteers (Group 1)
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	ESRD* (Group 5)	
		N=8	N=8	N=8	N=6	N=18
Cmax	Mean	336	277	334	303	356
(pg/mL)	SD	158	123	106	174	164
	CV%	47.1	44.4	31.9	57.4	46.1
AUClast	Mean	1180	847	2080	1940	821
(hr*pg/mL)	SD	428	276	1410	1560	288
	CV%	36.2	32.7	67.5	80.7	35.1
AUCinf	N[1]	7	4	7	6	12
(hr*pg/mL)	Mean	1630	1320	2730	3740	1020
	SD	485	320	1730	4970	400
	CV%	29.9	24.4	63.4	133	39.2
Tmax (hr)	Median	0.083	0.083	0.083	0.125	0.083
	Range	0.083-0.083	0.083-0.25	0.083-0.25	0.083-0.25	0.083-0.167
T1/2 (hr)	N[1]	7	4	7	6	12
	Mean	50.9	39.9	46.0	61.7	32.5
	SD	19.4	27.6	7.01	38.0	23.4
	CV%	38.1	69.1	15.2	61.6	72.1
CL/F (L/hr)	N[1]	7	4	7	6	12
	Mean	66.8	79.7	49.5	50.9	114
	SD	21.6	20.3	26.5	23.1	46.2
	CV%	32.3	25.4	53.6	45.4	40.6

(Source: Table 11-3, Study NVA237A2105 report)

Table 15. Summary of the statistical analysis of primary PK parameters

Parameter	RI group	Ratio vs HV (90% CI) Primary analysis	Ratio vs HV (90% CI) Sensitivity analysis
AUClast	Mild (Group 2)	1.58 (1.08, 2.31)	1.42 (1.08, 1.87)
(hr*pg/mL)	Moderate (Group 3)	0.91 (0.66, 1.26)	1.02 (0.78, 1.35)
	Severe (Group 4)	1.57 (0.89, 2.75)	2.21 (1.45, 3.36)
	ESRD (Group 5)	2.25 (1.59, 3.18)	2.07 (1.35, 3,19)
Cmax	Mild (Group 2)	1.04 (0.64, 1.71)	0.94 (0.68, 1.30)
(pg/mL)	Moderate (Group 3)	0.62 (0.39, 0.97)	0.76 (0.53, 1.10)
	Severe (Group 4)	1.04 (0.70, 1.53)	0.98 (0.76, 1.27)
	ESRD (Group 5)	0.88 (0.60, 1.28)	0.83 (0.56, 1.23)
CLr (L/hr)*	Mild (Group 2)	0.53 (0.41, 0.69)	0.62 (0.49, 0.79)
	Moderate (Group 3)	0.50 (0.36, 0.70)	0.46 (0.37, 0.58)
	Severe (Group 4)	0.29 (0.18, 0.45)	0.20 (0.14, 0.28)

* no urine collected for ESRD group

(Source: Table 11-6, Study NVA237A2105 report)

Urine PK Results

The key urine PK parameters are summarized in Table 16. The mean amount of NVA237 excreted into urine (Ae0-96h) decreased with increasing severity of RI, from 20.0 % of dose in healthy subjects to 8.43 % of dose in patients with severe RI. Mean T1/2, which could be determined based on urine excretion rate-time curves for most or all subjects per group, were similar across the RI groups and about 10 hours longer than in HV. Renal clearance (CLr) decreased with increasing severity of renal impairment as expected.

Table 16. Summary of urine PK parameters of glycopyrronium

PK parameter		Renally impaired subjects			Healthy volunteers (Group 1)
		Mild (Group 2)	Moderate (Group 3)	Severe (Group 4)	
		N=8	N=8	N=8	N=18
Ae0-96h	Mean	16.3	9.89	8.43	20.0
(µg) or (% dose)[1]	SD	4.39	3.71	4.28	6.38
	CV%	27.0	37.5	50.8	31.9
T1/2 (hr)	N[2]	7	7	8	17
	Mean	45.9	46.1	47.5	35.1
	SD	12.2	13.7	14.0	11.5
	CV%	26.6	29.7	29.6	32.6
CLr	Mean	14.2	10.4	4.88	23.0
(L/hr)	SD	4.52	2.70	2.63	7.50
	CV%	31.8	25.9	53.9	32.6

All values rounded to 3 significant digits; ESRD patients were not included as they did not produce urine. [1] Ae0-96h values in µg and % dose are the same as the dose is 100 µg.

[2] Reduced values of N provided for parameters that could not be estimated for all subjects/group

Source: PT-Table 14.2-4.10.3

(Source: Table 11-4, Study NVA237A2105 report)

Effect of dialysis

The effect of the 4-hour dialysis on the NVA237 plasma concentration time-profiles for the ESRD group and PK parameter statistical analysis are shown in Figure 7 and Table 17. Results indicate that mean plasma concentrations is lower in Period 2 (with dialysis) as compared to Period 1 (without dialysis). AUClast and Cmax were both reduced for ESRD subjects following inhalation of NVA237 in Period 2 with dialysis as compared Period 1 without dialysis.

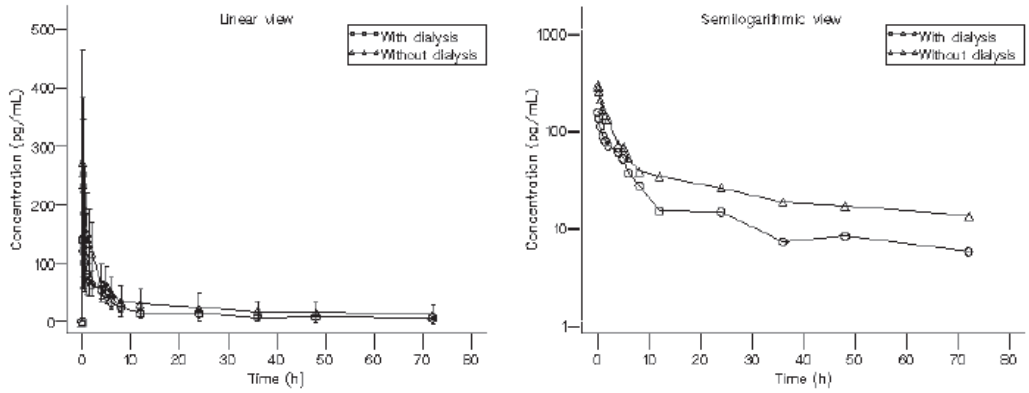


Figure 7. Arithmetic mean (SD) NVA237 plasma concentration time-profile for ESRD group without and with dialysis

(Source: Figure 11-2, Study NVA237A2105 report)

Table 17. Summary of statistical analysis of PK parameters for ESRD subjects with and without dialysis

Parameter	Period	LS Mean (90% CI)	Ratio Period 2 vs Period 1 (90% CI)
Cmax (pg/mL)	1	5.52 (5.44, 5.60)	
	2	4.92 (4.50, 5.34)	0.55 (0.35, 0.87)
AUClast	1	7.28 (7.05, 7.52)	
(hr*pg/mL)	2	7.00 (6.85, 7.14)	0.75 (0.54, 1.05)

Source: PT-Table 14.2-4.15
(Source: Table 11-7, Study NVA237A2105 report)

Conclusions

- In the sensitivity analysis, a moderate increase in NVA237 AUClast of 1.42 and 1.02 fold was estimated in subjects with mild and moderate RI respectively. An increase of 2.21 and 2.07 fold in AUClast was observed in subjects with severe RI and ESRD, respectively as compared to the entire control group.
- Cmax values were similar or even lower in each group of subjects with different degrees of RI as compared to the HVs.
- Renal clearance was reduced by ~ 40% to 50% in subjects with mild and moderate RI, and ~ 70% to 80% in subjects with severe RI as compared with HVs.
- NVA237 was partially cleared during a hemodialysis period of four hours (with an extraction ratio of 24.3%). AUClast and Cmax were reduced by 25% and 45% respectively for ESRD subjects in the treatment with dialysis.

Intrinsic Factor

Study CNVA237A2107

Title: An open-label study to investigate the pharmacokinetics of NVA237 following multiple once-daily inhaled doses in healthy Chinese subjects

Objectives

Primary: to assess the PK of NVA237 following multiple once-daily 50 mcg NVA237 inhalation 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. The study consisted of a screening period (Day -28 to Day -2), a baseline period (Day -1) and a treatment period of multiple dosing (Day 1 to Day 14) and PK sampling until Day 17 and a Study Completion evaluation on Day 17.

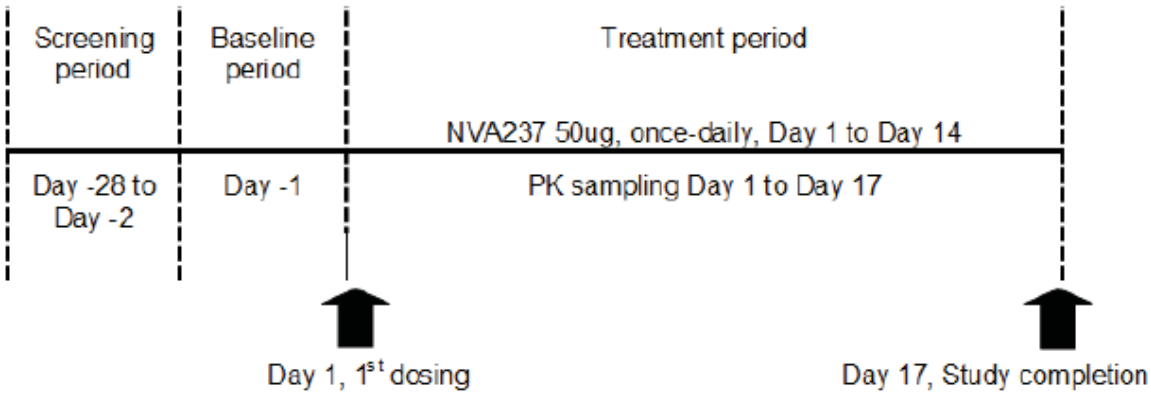


Figure 8. Study design

PK Sampling Schedule

Blood samples were collected on Days 1 and 14 at the following time points: predose, 5, 10, 15, 30 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose. Additional samples were collected at 36, 48, and 72 hours post-dose on Day 14. Trough PK samples were collected on Days 5, 7, 10 and 12 prior to drug inhalation.

Results

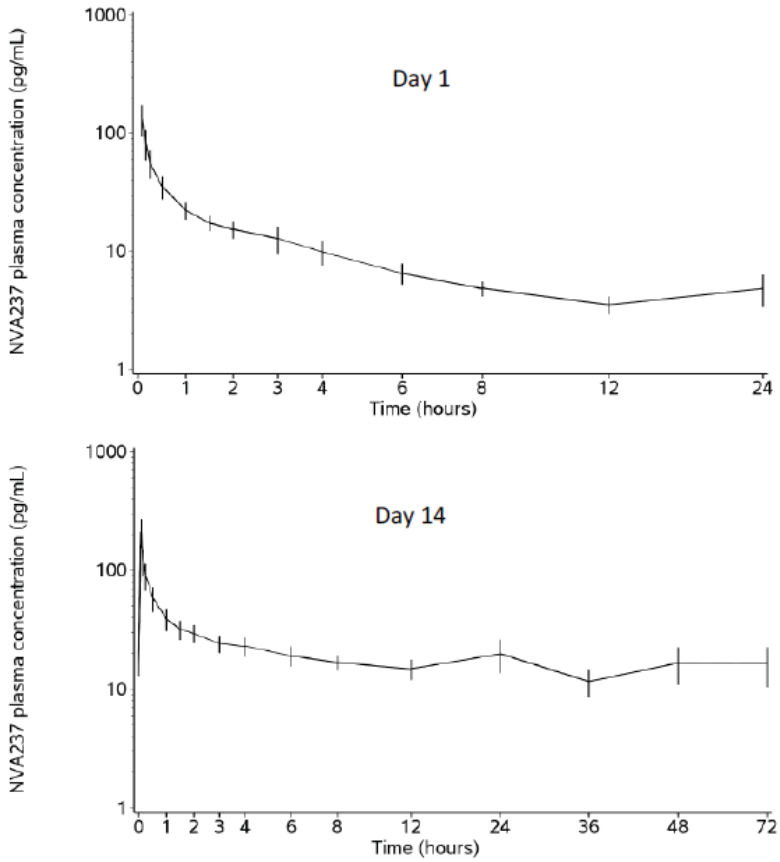


Figure 9. Arithmetic mean (SD) plasma concentration-time profiles of NVA237 on Day 1 and Day 14

(Source: Figure 11-1, Study NVA237A2107 report)

Table 18. PK parameters of NVA237 on Day 1

PK parameter (unit)	NVA237 50 µg Mean ± SD (% CV) [n]
AUC0-24h (hr*pg/mL)	185 ± 26.2 (14.2) [12]
Cmax (pg/mL)	134 ± 38.3 (28.7) [12]
Tmax (hour)**	0.08 (0.08-0.12) [12]

Source: Table 14.2-2.1

**Median (Min-Max) [n]

(Source: Table 11-3, Study NVA237A2107 report)

Table 19. PK parameters of NVA237 on Day 14

PK parameter (unit)	NVA237 50 µg Mean ± SD (% CV) [n]
Cmax,ss (pg/mL)	213 ± 57.1 (26.8) [12]
AUC0-24h,ss (hr*pg/mL)	511 ± 65.6 (12.8) [12]
Tmax (hr)**	0.08 (0.08-0.08) [12]
Cmin,ss (pg/mL)	13.5 ± 1.65 (12.2) [12]
Cav,ss (pg/mL)	21.3 ± 2.73 (12.8) [12]
T1/2,acc (hr)	37.7 ± 7.53 (20.0) [12]
Racc	2.80 ± 0.445 (15.9) [12]
Fluc (%)	931 ± 213 (22.9) [12]

Source: Table 14.2-2.1

**Median (Min-Max) [n]

(Source: Table 11-4, Study NVA237A2107 report)

Table 20. Statistical analysis of accumulation ratio for NVA237 PK parameters

		Adjusted geometric means		Ratio of geometric means		
Parameter(unit)	Treatment	Day 1	Day 14	Observed ratio	Lower 90% CI	Upper 90% CI
AUC0-24h (hr*pg/mL)	NVA237 50µg	183	507	2.77	2.54	3.01
Cmax (pg/mL)	NVA237 50µg	129	205	1.59	1.38	1.84

Source: Table 14.2-3.1

(Source: Table 11-5, Study NVA237A2107 report)

Conclusions

- Following 50 mcg QD NVA237 inhalation for 14 days in Chinese HV, median Tmax was 5 min on Days 1 and 14. PK steady state was achieved after 5 days and the mean effective T1/2 was 37.7±7.53 hrs. The observed accumulation ratios (Day14/Day1) were 2.77 and 1.59 for AUC and Cmax, respectively.

Phase 1 Bioavailability Study

Study CNVA237A2108

Title: A randomized, partly double-blind, two-part, study to determine the absolute bioavailability of inhaled NVA237 and to compare the pharmacodynamics,

pharmacokinetics, safety and tolerability of a single dose of inhaled NVA237 with other routes of administration in healthy subjects

Objectives

Primary

- **Part 1:** To determine the effectiveness of oral activated charcoal in reducing/blocking the gastrointestinal (GI) absorption of an oral administration of NVA237
- **Part 2:** To determine the absolute bioavailability of inhaled NVA237 in HVs

Secondary

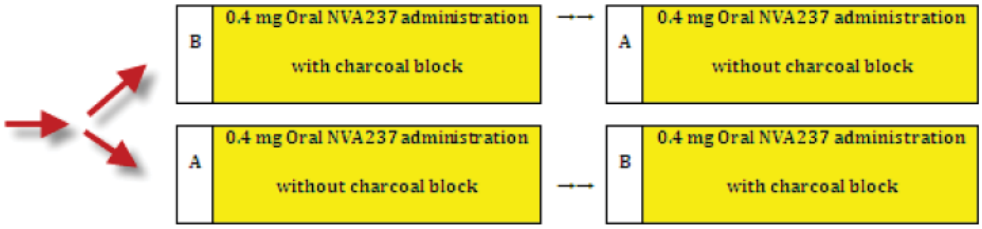
- **Part 1:**
  - To determine the PK of NVA237 after oral administration in healthy subjects with and without concomitant oral activated charcoal intake
  - To assess the safety and tolerability
- **Part 2**:
  - To determine the relative bioavailability of inhaled NVA237 given with oral activated charcoal relative to without oral activated charcoal
  - To investigate the effect of IV glycopyrrolate on heart rate as compared to placebo (key PD objective)
  - To assess the safety and tolerability

Study Design and Treatment Schedule: This study had two parts. The first part was a randomized, open-label, two-period, crossover study in healthy volunteers. The second part was a randomized, partially blind, four-period, two-sequence, crossover study in HVs (Figure 10).

Part 1 consisted of a 27-day screening period, 2 baseline days, 2 treatment periods followed by a study completion evaluation, 10 days after the last drug administration. Consecutive treatment periods were separated by a washout period of 10 to 21 days. Treatments were single doses of 400 mcg NVA237 administered orally with and without charcoal.

Part 2 consisted of a 27-day screening period, 4 baseline days, 4 treatment periods followed by a study completion evaluation, 10 days after the last drug administration. Consecutive treatment periods were separated by washout periods of 10 to 21 days. Treatments were single IV infusions of 120 mcg glycopyrrolate and IV placebo administered under double blind conditions in the first two periods followed by a single inhaled dose of 200 mcg NVA237 in Period 3 and a single inhaled dose of 200 mcg NVA237 with charcoal in Period 4.

Part 1



Part 2

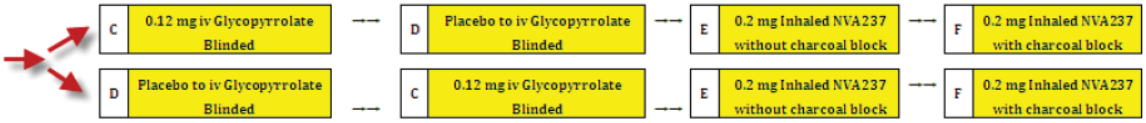


Figure 10. Study design of Part 1 and Part 2
(Source: Figure 9-1 and 9-2, Study NVA237A2108 report)

Table 21. Test product

Study drug and strength	Formulation control number	Batch number
NVA 237 50 µg capsules	6002280.003	X144GF
Matching placebo capsules	6001727.004	X137EF
Glycopyrrolate for injection	not applicable	8393C41
Dextrose 5% solution	not applicable	10I26G61, 10H26E05, 10K22E0W
Carbomix® (activated charcoal)	not applicable	10E05, 09102

(Source: Table 9-1, Study NVA237A2108 report)

PK Sampling Schedule:
Part 1:
Blood samples were collected at 0, 5, 10, 15, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hrs post-dose.
Urine samples were collected at 0, 0-4, 4-8 and 8-24 post-dose.
Part 2:
Blood samples were collected at 0, 5, 10, 15, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hrs post-dose.
Urine samples were collected at 0, 0-4, 4-8, 8-24, 24-48 and 48-72 post-dose.

PD assessment
Heart rate assessment: Part 2 of the study required continuous 24 hours Holter monitoring at Screening, Periods 1, 2 and 3.

PK Results
Part 1
A summary of the key PK parameters after oral administration of NVA237 without and with charcoal is presented in the table below. Results indicated the charcoal treatment was efficient in blocking at least 96% of the oral absorption of NVA237.

Table 22. Summary of key PK parameters of NVA237 after oral administration (Part 1)

PK parameter	Statistic	Oral NVA237 400 µg	
		without charcoal	**with charcoal**
		N=8	N=2, 3 or 10
Cmax (pg/mL)	Mean (SD)	78.8 (32.7)	10.5 (5.62) [1)]
	CV%	41.5	53.5
Tmax (h)	Median	2.50	1.00 [1)]
	(range)	(1.00 – 4.00)	(0.50 – 1.00)
AUClast (h*pg/mL)	Mean (SD)	432 (195)	21.1 (20.3) [1)]
	CV%	45.2	96.2
AUCinf (h*pg/mL)	Mean (SD)	456 (203)	43.5 (19.8) [2)]
	CV%	44.6	45.6
T1/2 (h)	Mean (SD)	2.77 (1.80)	1.68 (0.271) [2)]
(based on plasma data)	CV%	64.9	16.1
Ae0-24h (µg)	Mean (SD)	10.9 (4.70)	0.360 (0.558) [3)]
	CV%	43.1	154
CLr (L/h)	Mean (SD)	24.5 (6.86)	n/a
	CV%	(28.0)	

All values rounded to 3 significant digits; [1)] n= 3; [2)] n= 2; [3)] n= 10
(Source: Table 1, Study NVA237A2108 report)

Part 2
The PK profiles and key PK parameters after IV administration and inhalation are shown as below.

Following IV dosing, the systemic plasma clearance (CL) of NVA237 was on average 42.5 L/h and the mean renal clearance (CLr) was 26.0 L/h, which means that renal elimination accounted for about 61% of NVA237 systemic clearance, while non-renal mechanisms accounted for 39%. On average, 60.6% of the intravenous dose was recovered from the urine as parent drug.

The absolute bioavailability of orally inhaled NVA237 is about 40% based on AUCinf ratios.

For Flung, the fraction of systemic exposure due to lung absorption following inhalation of NVA237 is estimated between 86.4% (based on AUClast) and 97.1% (based on non-compartmental AUCinf data), and 95.9% (based on compartmental analysis). It is concluded that following oral inhalation, about 90% of systemic exposure of NVA237 is due to lung absorption while about 10% is due to gastrointestinal absorption.

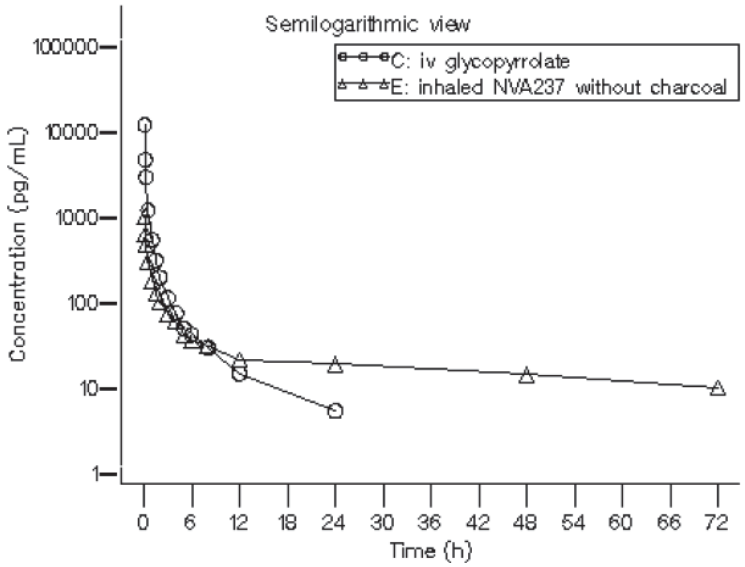


Figure 11. Arithmetic mean concentration-time profile of NVA237 after IV glycopyrrolate 120 mcg and inhaled NVA237 200 mcg without charcoal
(Source: Figure 1, Study NVA237A2108 report)

Table 23. Summary of key PK parameters of NVA237 after IV infusion and inhalation with and without charcoal (Part 2)

Parameter	Statistic	i.v. glycopyrrolate 120 µg	Inhaled NVA237 200 µg	
			without charcoal	with charcoal
		N=18	N=18	N=17
Cmax (pg/mL)	Mean (SD)	9720 (2230)	858 (391)	729 (297)
	CV%	22.9	45.6	40.7
Tmax (h)	Median	0.083	0.083	0.083
	(range)	(0.08 – 0.12)	(0.07 – 0.17)	(0.08 – 0.12)
AUClast (h*pg/mL)	Mean (SD)	2840 (450)	1541 (259)	1360 (309)
	CV%	15.9	16.8	22.8
AUCinf (h*pg/mL)	Mean (SD)	2890 (453)	2090 (462) [1)]	2050 (566) [2)]
	CV%	15.7	22.1	27.6
T1/2 (h)	Mean (SD)	6.16 (1.03)	52.5 (12.7) [1)]	57.2 (17.4) [2)]
(based on plasma data)	CV%	16.7	24.2	30.5
CL (L/h)	Mean (SD)	42.5 (6.36)	99.7 (20.0) [1), 3)]	n/a
	CV%	15.0	20.0	
Vz (L)	Mean (SD)	376 (80.0)	7310 (1492) [1), 4)]	n/a
	CV%	21.3	20.4	
Vss (L)	Mean (SD)	82.7 (21.7)	n/a	n/a
	CV%	26.2		
Ae0-72h (µg)	Mean (SD)	72.7 (20.9) [5)]	30.4 (8.26)	27.2 (6.96)
	CV%	28.8	27.2	25.6
CLr (L/h)	Mean (SD)	26.0 (8.54)	23.1 (7.46)	23.7 (5.42)
	CV%	32.8	32.3	22.9

All values rounded to 3 significant digits (except Tmax); [1)] n=12; [2)] n=13; [3)] CL/F; [4)] Vz/F; [5)] n=20
(Source: Table 2, Study NVA237A2108 report)

PD Results

There were no tachycardic effects on heart rate. There were no apparent relationships between systemic drug concentrations of NVA237 and the effects on heart rate.

Conclusions

- Oral activated charcoal was effective in blocking the oral absorption of NVA237
- The disposition of NVA237 differed between the routes of administration. The terminal elimination phase was much longer after NVA237 inhalation without or with charcoal (mean T1/2 was 52.5 h and 57.2 h respectively) than after intravenous dosing (mean T1/2: 6.2 h) and oral administration without charcoal (mean T1/2: 2.8 h).
- The absolute bioavailability of orally inhaled NVA237 (Fabs) was estimated to be about 40%.
- About 90% of systemic exposure following inhalation of NVA237 via the Concept1 device is due to lung absorption and 10% is due to gastrointestinal absorption.
- About 36% of the inhaled dose was deposited and absorbed in the lungs following inhalation using Concept1.
- After IV administration, about 61% of systemic clearance of NVA237 was accounted for by renal elimination while 39% of systemic clearance was due to non-renal mechanisms.
- The metabolite CJL603 (M9, inactive metabolite) was of minor importance afterIV administration. CJL603 is formed from the swallowed dose fraction of orally inhaled NVA237 (Study NVA237A2108 addendum 1).
- NVA237 was safe and well tolerated in all the dose forms used in this study.
- There were no tachycardic effects on heart rate.

Extrinsic Factor

Study CNVA237A2109

Title: A randomized, open label, two-period, crossover study to determine the effect of oral doses of cimetidine on the pharmacokinetics of a single inhaled dose of NVA237 upon co-administration in healthy adult subjects.

Objectives

Primary: to determine the effect of oral doses of cimetidine (800 mg b.i.d) on the pharmacokinetics of a single inhaled dose of NVA237 (100 mcg) upon co-administration in healthy adult subjects.

Secondary: to determine safety and tolerability of NVA237 single inhaled dose (100 mcg) in the presence of cimetidine (800 mg BID) in healthy subjects.

Study Design and Treatment Schedule:

Both NVA237 and cimetidine are primarily eliminated through the kidney and active tubular secretion contributes to their elimination. NVA237 has been identified as a substrate of OCT2 and cimetidine is known to be an efficient inhibitor of OCT2 at doses of 800 mg and above. Inhibition of the OCT2 mediated clearance pathway of NVA237

by cimetidine is likely to lead to a decrease in clearance and, as a consequence, it may lead to an increase in systemic exposure to NVA237.

This is an open-label, randomized, single-dose, two-period crossover study in HVs. Each subject participated in a 28 day screening period, two baseline periods (one before each treatment period), two treatment periods with a washout period between 7 and 10 days between the two treatment periods, and a study completion evaluation approximately 72 hours after the last study drug administration.

All subjects received both treatments in random order. These were defined as:

- Treatment A: A single inhaled dose of NVA237 100 mcg (given as 2 x 50 mcg dry powder capsules, i.e. two inhalations using one capsule each) on Day 1 using the Concept1 device followed by PK assessment till 72 hours post dose (Day 4).
- Treatment B: cimetidine 800 mg (given as 2 x 400 mg tablets; Tagamet®) BID oral administration for 6 days + single inhaled dose of NVA237 100 mcg (given as 2 x 50 mcg dry powder capsules) on Day 4 using the Concept1 device followed by PK assessment till 72 hours post dose (Day7).

Subjects were randomized to one of the following sequences in 1:1 ratio:
Sequence 1: Treatment A in first period and Treatment B in second period
Sequence 2: Treatment B in first period and Treatment A in second period

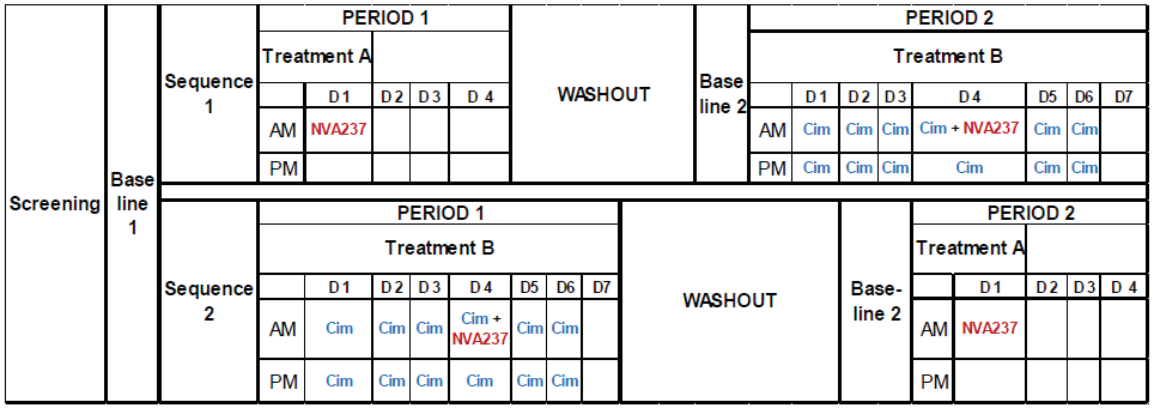


Figure 12. Study Design
(Source: Figure 9-1, Study NVA237A2109 report)

Table 24. Test Product

Treatment	Device	Strength	Batch #
NVA237 100 mcg (2 x 50 mcg dry powder Capsules)	Concept1	50 mcg dry powder capsules	X287ME
cimetidine 800 mg (2 x 400 mg tablets; Tagamet), Oral	NA	400 mg tablets	92306
Matching placebo capsules	**NA**	**NA**	X006AF

PK Sampling Schedule

Blood samples

NVA237: blood samples were taken at pre-dose, 5, 10, 15, 30 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after NVA237 administration.

Cimetidine: blood samples were taken:

- Days 1-6: pre-dose.
- Day 7: pre-dose, 5, 10, 15, 30 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post dose.

Urine samples: urine was collected at pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hours post-dose (after NVA237 administration in Treatments A and B).

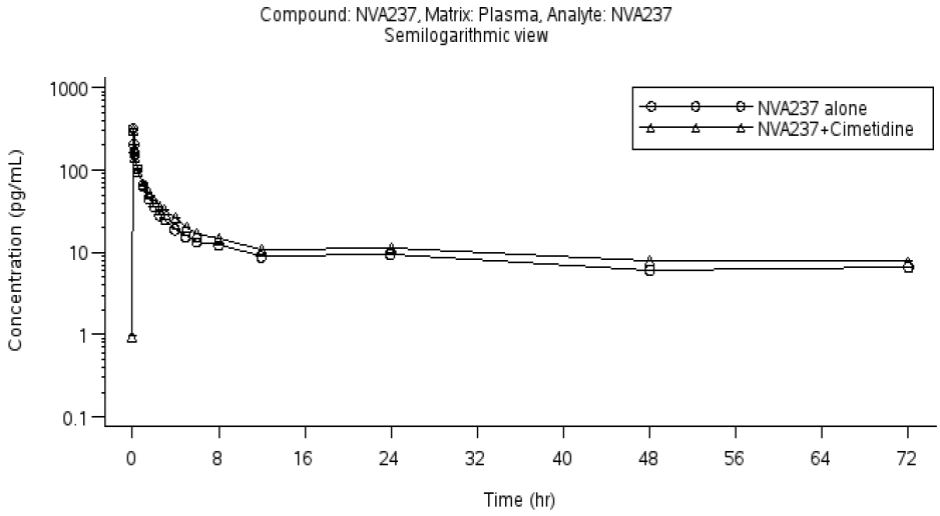
Results

Plasma PK

A total of 20 HVs were enrolled into the study, all of whom completed. The concentration-time profiles and key PK parameters for NVA237 given alone and with cimetidine are shown as below (Figure 13, Table 25).

NVA237 was systemically available shortly after inhalation (median Tmax is ~5 min) and plasma concentrations decreased rapidly thereafter for all groups. PK steady state of cimetidine was reached at Day 3 (Figure 14). The plasma concentration-time profiles for NVA237 of two treatment groups were similar.

The average Cmax of NVA237 was similar for the two treatments. Overall the total systemic exposure (AUClast) was slightly higher when NVA237 was coadministered with cimetidine (919 hr*pg/mL) than when administered alone (771 hr*pg/mL). The terminal elimination T1/2 of NVA237 could only be determined for less than half the subjects under each treatment regimen. Mean T1/2 was 45.3 h when NVA237 was administered alone and 52.9 h when NVA237 co-administered with cimetidine.



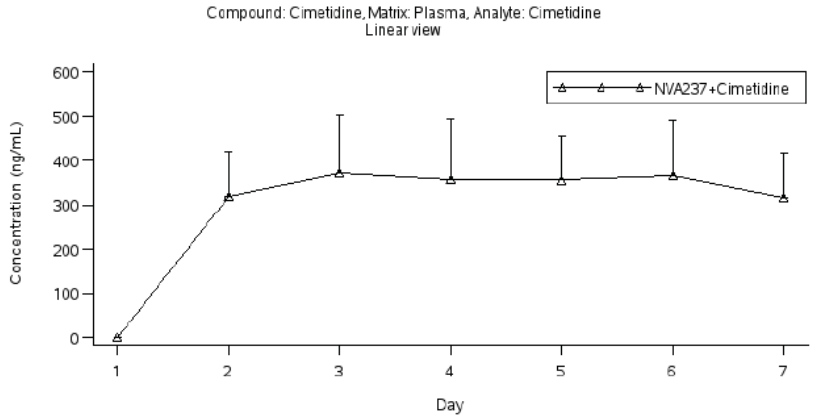
Source: PT-Figure 14.2-1.1; Treatment A: NVA237 100 µg; Treatment B: cimetidine 800 mg b.i.d. oral administration for 6 days + single inhaled dose of NVA237 100 µg on Day 4.

Figure 13. Arithmetic mean (SD) plasma concentration-time profiles for NVA237
(Source: Figure 11-1, Study NVA237A2109 report)

Table 25. Summary of key plasma PK parameters of NVA237

Treatment	Statistic	Cmax (ng/mL)	AUClast (hr*pg/mL)	AUC0-24h (hr*pg/mL)	AUCinf (hr*pg/mL)	CL/F (L/hr)	Tmax (hr)	T1/2 (hr)
NVA237 alone	N	20	20	20	7	7	20	7
	Mean (SD)	323 (149)	771 (251)	434 (133)	1000 (421)	121 (67.6)	-	45.3 (22.2)
	CV%	46.0	32.6	30.7	41.9	55.8	-	48.9
	Geo-mean	287	729	415	919	109	-	39.2
	Median	297	778	400	966	104	0.083	50.2
	Range	68.7, 595	308, 1290	203; 708	382, 1700	58.9, 262	0.067, 0.133	11.9, 77.2
Cimetidine + NVA237	n	20	20	20	9	9	20	9
	Mean (SD)	312 (151)	919 (235)	499 (109)	1390 (330)	75.4 (17.6)	-	52.9 (19.9)
	CV%	48.5	25.5	21.9	23.7	23.4	-	37.6
	Geo-mean	270	888	487	1360	73.6	-	49.8
	Median	279	927	495	1370	73.1	0.083	45.7
	Range	46.4, 599	472, 1430	263; 690	957, 1910	52.4, 105	0.067, 0.117	32.2, 81.1

Note: Geo = Geometric
(Source: Table 11-2, Study NVA237A2109 report)



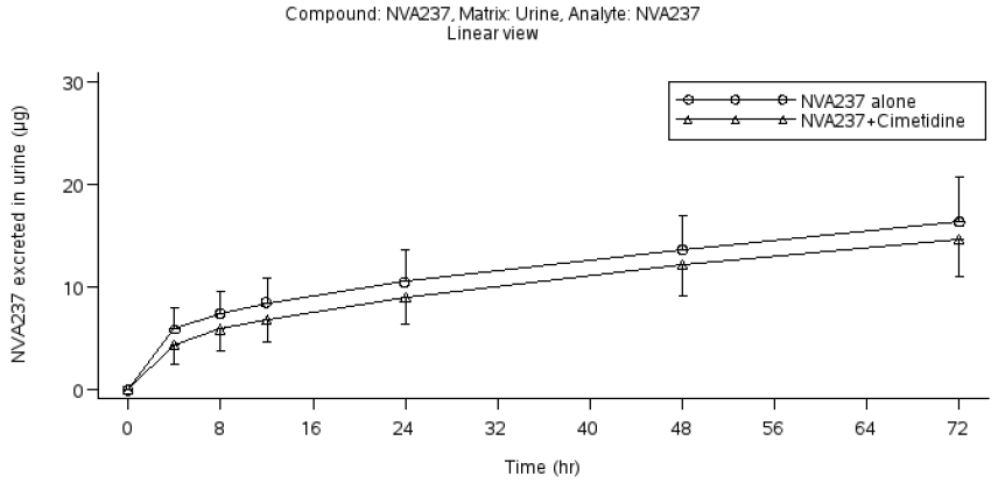
Source: PT-Figure 14.2-1.2; cimetidine 800 mg b.i.d. oral administration for 6 days + single inhaled dose of NVA237 100 µg on Day 4.

Figure 14. Plasma concentration-time profiles of cimetidine
(Source: Figure 11-2, Study NVA237A2109 report)

Urine PK

The mean cumulative urine excretion of NVA237 versus time per treatment and urine PK parameters were shown as below (Figure 15, Table 26).

The amount of NVA237 excreted in urine over the 72-hour period was very similar for the two treatment groups. Mean Ae0-72h of NVA237 accounted for 16.4% and 14.7% of the dose for NVA237 alone and co-administered with cimetidine, respectively. The elimination T1/2 of NVA237 could be determined from urine excretion rate-time curve for 8 and 12 of the 20 subjects when receiving NVA237 alone and co-administered with cimetidine and mean T1/2 was 36.1 h and 43.5 h, respectively.



Source: PT Table 14.2-1.6; Treatment A: NVA237 100 µg; Treatment B: cimetidine 800 mg b.i.d. oral administration for 6 days + single inhaled dose of NVA237 100 µg on Day 4.

Figure 15. Arithmetic mean (SD) cumulative urine excretion of NVA237 per treatment
(Source: Figure 11-3, Study NVA237A2109 report)

Table 26. Summary of urine PK parameters of NVA237 and cimetidine

Treatment	Statistic	T1/2 (hr)	Ae0-72h (µg)	Ae0-72h (% of dose)	CLr (L/hr)
NVA237 alone	N	8	18	18	18
	Mean (SD)	36.1 (16.9)	16.4 (4.31)	16.4 (4.31)	21.2 (4.14)
	CV%	46.7	26.2	26.2	19.5
	Geo-mean	33.2	15.9	15.9	20.8
	Median	30.8	15.7	15.7	20.5
	Range	18.0; 66.3	9.79; 25.7	9.79; 25.7	14.7; 30.5
Cimetidine + NVA237	N	12	20	20	20
	Mean (SD)	43.5 (11.0)	14.7 (3.66)	14.7 (3.66)	16.5 (4.17)
	CV%	25.3	24.9	24.9	25.2
	Geo-mean	42.1	14.2	14.2	16.0
	Median	46.9	15.6	15.6	16.6
	Range	28.2; 57.8	7.64; 19.8	7.64; 19.8	9.20; 25.0

Ae0-72h values in % of dose are the same as the µg values as the dose is 100 µg.
(Source: Table 11-3, Study NVA237A2109 report)

Statistical analysis

The results of the statistical analysis of the PK parameters Cmax, AUClast, CLr, AUCinf, AUC0-24h and Ae0-72h were summarized as below (Table 27). AUClast of NVA237 showed 1.22-fold (90% CI 1.12-1.32) increase when NVA237 was given with cimetidine

compared to when given alone, while NVA237 Cmax remained similar (GMR of 0.94, 90% CI 0.82-1.07) for both treatments.

It should be notes that AUCinf values could only be estimated for 9 and 7 of the 20 subjects in the test (co-administration) and reference treatment (NVA237 alone). The statistical results for AUCinf should be interpreted with caution.

Table 27. Estimated geometric mean ratios (test/reference) and 90% CI for NVA237 PK parameters

	Adjusted geometric mean		Ratio of geometric means		
Parameter (Unit)	Test	Reference	Estimate	Lower 90% CI	Upper 90% CI
Primary parameters					
Cmax (pg/mL)	270	287	0.94	0.82	1.07
AUClast (hr*pg/mL)	888	729	1.22	1.12	1.32
CLr (L/hr)	16.0	20.8	0.77	0.70	0.85
Secondary parameters					
AUC0-24h (hr*pg/mL)	487	415	1.17	1.09	1.27
AUCinf (hr*pg/mL)	1190	1210	0.99	0.82	1.19
Ae0-72h (µg)	14.2	15.6	0.91	0.83	1.00

Reference: 100 µg NVA237 administered alone.
Test: 100 µg NVA237 co-administered with cimetidine (800mg b.i.d.).
(Source: Table 11-4, Study NVA237A2109 report)

Conclusions

- A slight increase of NVA237 total exposure (AUClast) by 22% was observed when NVA237 was co-administered with cimetidine, which may correlated with a slight decrease in renal clearance (CLr) of NVA237 by 23%.
- Cmax of NVA237 was not affected by co-administration of cimetidine.
- Based on the magnitude of the PK changes, no relevant drug interaction is expected when NVA237 is co-administered with cimetidine.

PK/PD Study in Healthy Subjects

Study CNVA237A2110

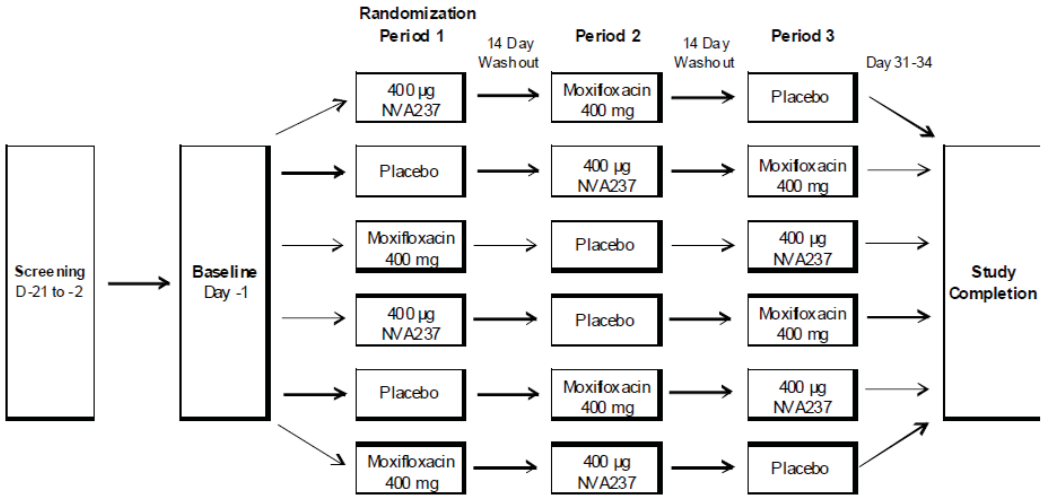
Title: A randomized, partially-blinded, 3- period cross over study to evaluate the effects of single dose NVA237 on the corrected QT interval in healthy volunteers, using moxifloxacin and placebo as positive and negative controls

Objectives

Primary: to evaluate the effect of a single inhaled dose of 400 mcg NVA237 on the QTcF interval in HVs

Secondary: to evaluate the effect of a single inhaled dose of 400 mcg NVA237 in HVs on other ECG parameters and blood pressure, PK, safety and tolerability

Study Design and Treatment Schedule:
This was a randomized, partially-blinded, single dose, placebo and positive (moxifloxacin) controlled three way cross-over study in HVs (Figure 16). On Day 1, subjects were randomized to one of the 6 treatment sequences, where they received either a single inhaled dose of 400 mcg NVA237, its matching placebo given in a double blind fashion or a single oral dose of open-label 400 mg moxifloxacin. Following dosing, ECG recordings, safety and PK assessments were conducted up to 24 hours post dose.



A period of at least 14 days (maximum of 21 days) separated each dose.

Figure 16. Study design
(Source: Figure 9-1, Study CNVA237A2110 report)

Table 28. Test product

Treatment	Device	Strength	Batch #
NVA237 400mcg (8 capsules)	Concept 1	50 mcg capsules	X144GF
NVA237 placebo (8 capsules)	Concept 1	NA	X137EF
Moxifloxacin, oral	NA	400 mg tablet	(b) (4) lot # 540232P

PD Assessment
25-hour Holter ECG recordings were used for QT evaluations. These were collected starting 1 hour pre-dose until 24 hours post-dose on dosing days (Day 1 for all three periods). Triplicate readings were taken, separated by 1 minute intervals.

The time windows that were used for QT analysis in triplicates were: 1 hr pre-dose, 45 min pre-dose, 30 min pre-dose, 15 min pre-dose, pre-dose and post-dose at 5 min, 15 min, 30 min, 60 min, 90 min, and 2, 3, 4, 5, 6, 8, 12 & 24 hr post-dose. Triplicates were separated by 1 minute intervals.

PK Sampling Schedule

PK samples were taken on Day 1 after the administration of NVA237, placebo, or moxifloxacin: predose, 5 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.

Results

Primary PD results

The primary PD variable was the change from period baseline in the QTcF interval, where period baseline was the average of the -60, -45, -30, -15 and 0 (pre-dose) hours readings. Results indicated there is no statistical evidence of a significant QTcF prolongation with NVA237 compared to placebo (Figure 17).

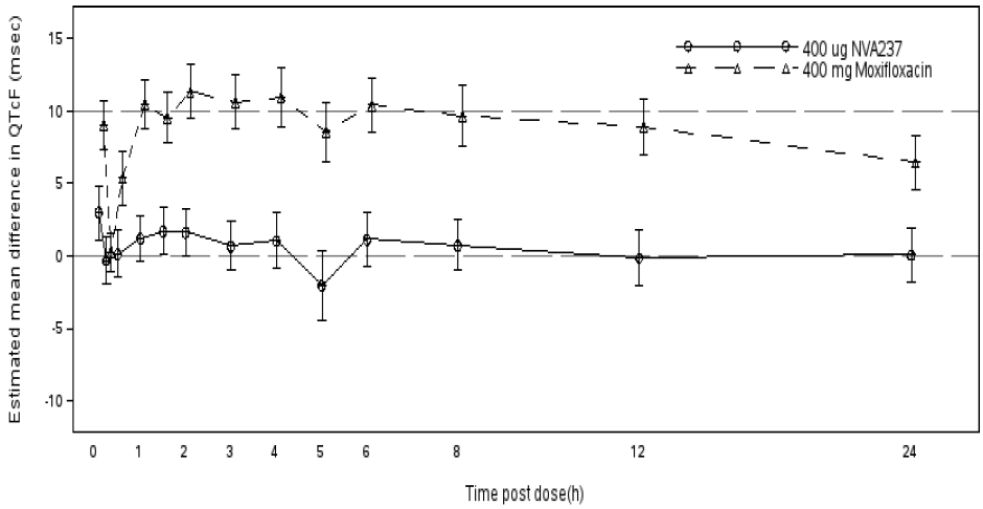


Figure 17. Estimated mean difference of NVA237 and moxifloxacin vs placebo for change from baseline in QTcF by time-point

(Source: Figure 11-1, Study CNVA237A2110 report)

PK results

The mean plasma concentration-time-profile for NVA237 was shown in Figure 18, and a summary of the plasma PK parameters after a single dose inhalation of NVA237 400 mcg are presented in Table 29.

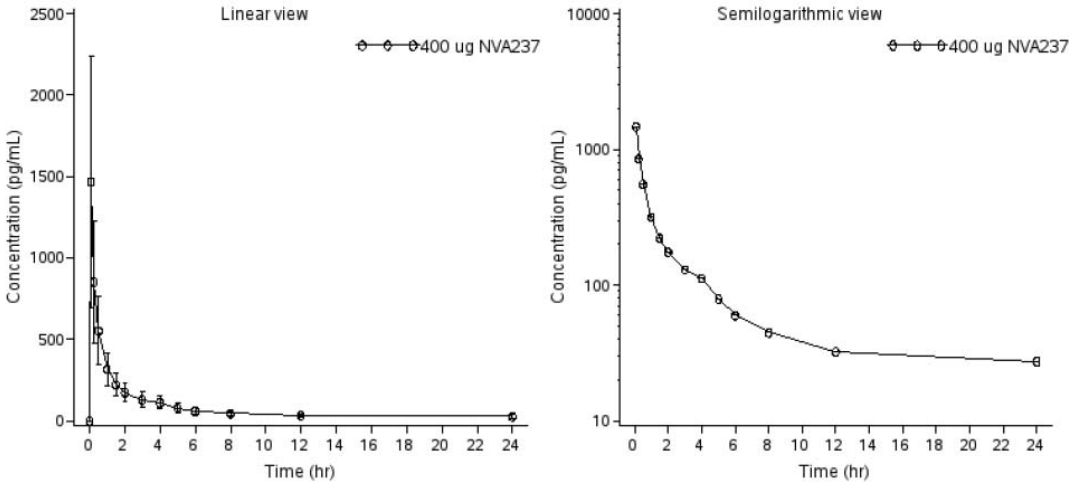


Figure 18. Arithmetic mean (SD) NVA237 plasma concentration-time profiles
(Source: Figure 11-4, Study CNVA237A2110 report)

Table 29. Summary of NVA237 PK parameters

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

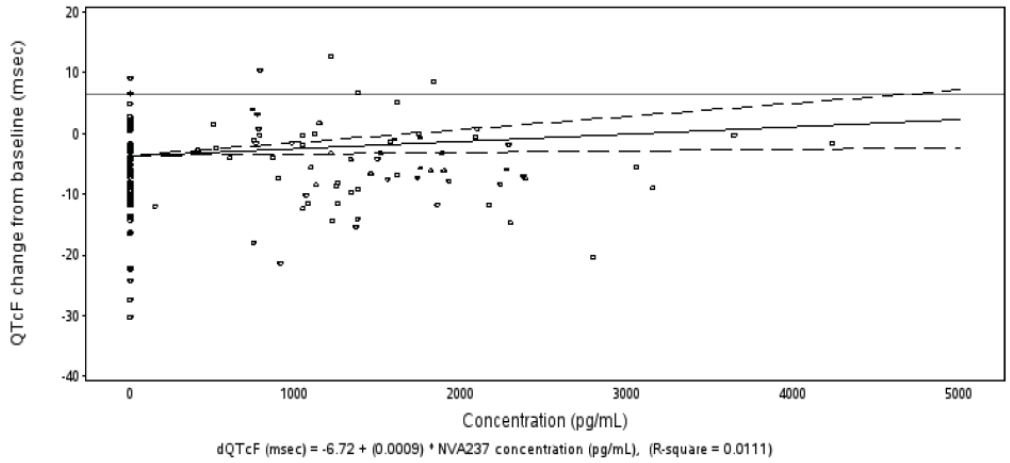
(Source: Table 11-7, Study CNVA237A2110 report)

PK-PD relationship

The NVA237 Cmax versus the corresponding change from baseline in QTcF at Tmax are presented in Figure 19 while the NVA237 Cmax and difference (NVA237-placebo) for corresponding change from baseline in QTcF at Tmax are shown in Figure 20.

There was no evidence of an exposure-response relationship between the NVA237 Cmax and treatment effect on the QTcF at Tmax after a single dose of 400 mcg of NVA237. Similarly there was no evidence for an exposure-response relationship between the NVA237 plasma concentration and treatment effect on the other cardiac parameters (QTcB and heart rate) at Tmax.

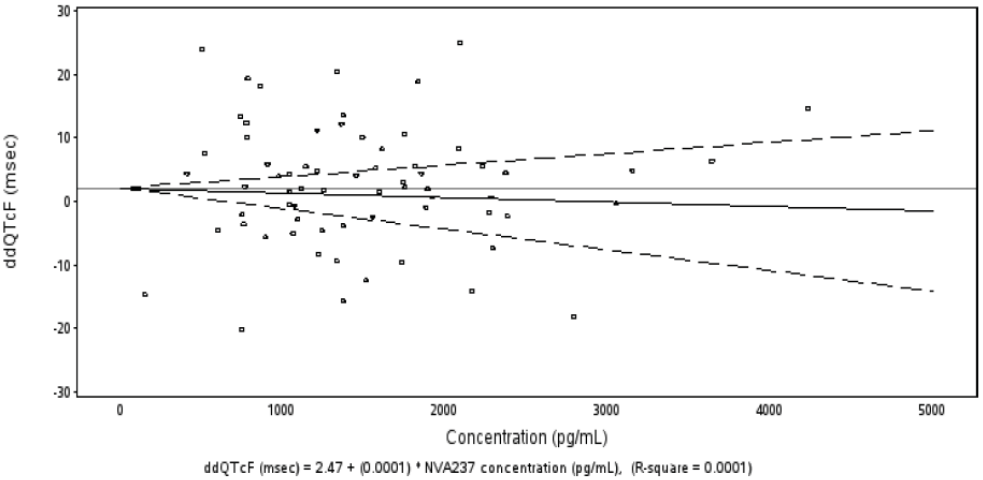
Likewise there was no evidence of an exposure-response relationship between either the individual NVA237 concentration or the total systemic exposure (AUClast) and an effect on the cardiac parameters (QTcF, QTcB and heart rate).



All observations under placebo and NVA237 are shown where the concentration for placebo is assumed to be zero. The solid regression line describes the linear relationship between the NVA237 plasma concentration (placebo taken as zero concentration) and cardiac parameter change from baseline at Tmax., with dotted lines showing the corresponding lower and upper 90% confidence band. The horizontal line is drawn at 10 msec + the estimated intercept.

Figure 19. The relationship between change from baseline in QTcF (dQTcF) at Tmax and NVA237 Cmax

(Source: Figure 11-5, Study CNVA237A2110 report)



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

Figure 20. The relationship between the difference between NVA237 and placebo for change from baseline in QTcF (ddQTcF) at Tmax and NVA237 Cmax

(Source: Figure 11-6, Study CNVA237A2110 report)

Conclusions

- A single dose of 400 mcg of NVA237 had no clinically relevant effect on the corrected QTcF interval. The mean effect and upper limit of the two-sided 90% CI both being below the respective thresholds of 5 ms and 10 ms.
- The positive control, moxifloxacin showed the expected clinical effect on QTcF interval thereby validating the study results.

- The effect on the QTcB interval was consistent with that on the QTcF interval.
- There was no evidence of an exposure-response relationship between systemic exposure (AUClast, Cmax) to NVA237 at a dose of 400 mcg and the effect of NVA237 on the QTcF as well as on the other cardiac parameters QTcB and heart rate.

For further details refer to QT/IRT review for NDA207923.

Dose-Ranging Study

Study CNVA237A2205

Title: A randomized, double-blind, placebo-controlled, 4 period incomplete block cross-over, multi-center, multiple dose (7 days) dose-ranging study to assess the efficacy and safety of 4 doses of NVA237 in patients with stable COPD, compared to seven days treatment with tiotropium (18mcg once daily, open label) as an active control

Objectives:

Primary: to evaluate the efficacy (trough FEV1, mean of 23h15min and 23h45 min postdose) of NVA237 in COPD patients following 7-day treatment of NVA237 12.5, 25, 50, and 100 mcg QD.

Secondary:

- To evaluate the efficacy of NVA237 (FEV1 and FVC) on Days 1 and 7.
- Safety and tolerability

Study Design and Treatment Schedule:

This was a placebo controlled study with an active control arm, of an incomplete block cross-over design (Table 30). Eligible patients who underwent a washout period from any prohibited medication were randomized to one of the available treatment sequences. At this point they began the first of four double-blind (open-label for tiotropium) 7 day treatment periods. Patients were assessed on Day 1 and Day 7 of each treatment period. There was a washout period of seven days between each treatment period. Treatments were placebo, tiotropium bromide (18 mcg), NVA237 12.5, 25, 50 and 100 mcg.

Table 30. Study design

Period	Screening	Treatment I (7 days)	Wash-out (7 days)	Treatment II (7 days)	Wash-out (7 days)	Treatment III (7 days)	Wash-out (7 days)	Treatment IV (7 days)	
Visit	1 2	3 4* 5	6*	7 8* 9	10*	11 12* 13	14*	15 16* 17	18*
Day	-14 -1	1 2 7	8	15 16 21	22	29 30 35	36	43 44 49	50
Randomization		X							
Study completion									X
Treatment Groups		NVA 12.5 µg or NVA 25 µg or NVA 50 µg or NVA 100 µg or Placebo or Tiotropium		NVA 12.5 µg or NVA 25 µg or NVA 50 µg or NVA 100 µg or Placebo or Tiotropium		NVA 12.5 µg or NVA 25 µg or NVA 50 µg or NVA 100 µg or Placebo or Tiotropium		NVA 12.5 µg or NVA 25 µg or NVA 50 µg or NVA 100 µg or Placebo or Tiotropium	

*: Visit 4, 6, 8, 10, 12, 14, 16 and 18 are the 23 hours 15 mins and 23 hours 45 mins post-dose spirometry visits

(Source: Table 9-1, Study NVA2372205 report)

Table 31. Test product using Concept 1 device

Drug	Batch number
Placebo	X016 0107
NVA237 12.5 µg	X223 0507
NVA237 25 µg	X010 0107
NVA237 50 µg	X008 0107
NVA237 100 µg	X011 0107

Tiotropium bromide 18 mcg delivered via the Handihaler®.
(Source: Table 1, Study NVA237A2205 report)

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

Efficacy Endpoint
- Primary: Trough FEV1 at Day 7, defined as the mean of two measurements at 23 h 15 min and 23 h 45 min post dosing.
- Secondary: trough FEV1 after 1 day of treatment, FEV1 over time, AUC of FEV1, peak FEV1 and FVC and FEV1 and FVC at individual timepoints on day 1 and day 7.

Primary Efficacy Results
Increasing doses of NVA237 resulted in increased LS mean trough FEV1 values at Day 7 suggesting a dose-response relationship. Both the 50 and 100 mcg NVA237 doses resulted in trough FEV1 values greater than that set for a clinically relevant effect (120 mL). All doses of NVA237 resulted in significantly greater LS mean trough FEV1 values than placebo at Day 7 (Table 32).

Table 32. Analysis of covariance of trough FEV1 (L) at Day 7

	N	LS Means	SE	95% CI	p-value (two sided)
Treatment effect					
NVA237 12.5 µg	55	1.317	0.0145	(1.289 - 1.346)	-
NVA237 25 µg	51	1.333	0.0151	(1.303 - 1.362)	-
NVA237 50 µg	53	1.374	0.0148	(1.345 - 1.403)	-
NVA237 100 µg	53	1.385	0.0148	(1.355 - 1.414)	-
Placebo	49	1.243	0.0156	(1.212 - 1.273)	-
Tiotropium bromide	55	1.370	0.0145	(1.341 - 1.398)	-
Treatment contrast (Primary Analysis)					
NVA237 100 µg – Placebo[d]		0.142	0.0215	(0.089 - 0.195)	<0.0001*
NVA237 50 µg – Placebo[d]		0.131	0.0219	(0.078 - 0.185)	<0.0001*
NVA237 25 µg – Placebo[d]		0.090	0.0217	(0.037 - 0.143)	0.0002*
NVA237 12.5 µg – Placebo[d]		0.075	0.0213	(0.023 - 0.127)	0.0020*
Treatment contrast (Secondary Analysis)					
NVA237 100 µg - Tiotropium bromide		0.015	0.0208	(-0.026 - 0.056)	0.4732
NVA237 50 µg - Tiotropium bromide		0.004	0.0209	(-0.037 - 0.046)	0.8325
NVA237 25 µg - Tiotropium bromide		-0.037	0.0211	(-0.079 - 0.004)	0.0801
NVA237 12.5 µg - Tiotropium bromide		-0.052	0.0207	(-0.093 - -0.012)	0.0121*
Tiotropium bromide – Placebo		0.127	0.0214	(0.085 - 0.169)	<0.0001*

LS = Least squares, SE = standard error of the mean, CI = confidence interval

ANCOVA: Trough FEV_1 at Day 7 = patient effect + period effect + treatment effect + (period) baseline FEV_1 + error.

[d] 95% confidence intervals for NVA doses versus placebo are based on a single step Dunnett procedure. For the same contrasts, 2 sided p-values are multiplicity adjusted based on a stepwise Dunnett procedure. All other confidence intervals for treatment contrasts and corresponding p-values are exploratory and calculated without accounting for multiplicity.

*p-value of <0.05

Source: Table 14.2-1.3

(Source: Table 11-5, Study NVA237A2205 report)

Conclusions

An obvious dose response relationship was observed at doses ranging 12.5 to 100 mcg QD. 50 and 100 mcg QD NVA237 doses resulted in a clinically relevant effect.

Reviewer's comments:

All tested dosing regimens were evaluated in another dose ranging study, Study NVA237A2208, in which both QD and BID regimens were investigated.

Dose-Ranging Study

Study NVA237A2208

Title: A randomized, double-blind, placebo-controlled, 2-period, cross-over study to assess the efficacy and safety of differing doses of NVA237 administered either once daily or twice daily, in patients with moderate to severe chronic obstructive pulmonary disease

Objectives:

Primary Objective: To evaluate the relationship of incremental doses of NVA237 QD and BID and their effect on trough FEV1 after 28 days of treatment

Secondary Objectives:

- To evaluate the magnitude of any difference of effect between the same total daily doses of NVA237 by comparing QD and BID.
- To evaluate the relationship of incremental doses of NVA237 QD and BID and their effect on AUC0-24 h FEV1 after 28 days of treatment.
- To evaluate dose response relationships of different doses/regimens of NVA237.
- Safety and tolerability.

Study Design and Method:
This was a multicenter, double-blind, randomized, dose finding trial in patients with stable moderate to severe COPD and a smoking history of at least 10 pack years utilizing an eight treatment, two-period (29 days each), balanced incomplete block design where the doses were delivered once or twice daily (Table 33). The 8 doses and regimens of NVA237 in this study were:

• 12.5 mcg QD
• 12.5 mcg BID
• 25 mcg QD
• 25 mcg BID
• 50 mcg QD
• 50 mcg BID
• 100 mcg QD
• Placebo to NVA237

NVA237 and placebo was provided as inhalation powder-filled capsules with the Concept1 device. Patients were randomized to 16 independent sequences (Table 34, 35). There was an 8 day screening/run-in period. Treatment period 1 was for 29 days with a 7 day washout-period and then followed by treatment period 2 for 29 days. Of the 388 randomized patients, 385 received at least one dose of study drug. The number of patients in each treatment sequence was comparable. No PK samples were collected.

Table 33. Study Design

Period	Pre-screening	Screening/ Run-in	Period 1	Wash-out period	Period 2
Visit	1	2	3-10		11-18
Day	-15 to -9	-8	29 days	7 days*	29 days
*Day 1 of washout period is Day 29 of Period 1					

(Source: Table 9-1 Study Design, Study NVA237A2208 report.)

Table 34. Treatment Sequences of Study NVA237A2208

Treatment sequence	Treatment in Period 1	Treatment in Period 2
1	12.5 µg once daily	50 µg once daily
2	50 µg once daily	12.5 µg once daily
3	12.5 µg once daily	25 µg twice daily
4	25 µg twice daily	12.5 µg once daily
5	placebo	50 µg twice daily
6	50 µg twice daily	placebo
7	placebo	100 µg once daily
8	100 µg once daily	placebo
9	12.5 µg twice daily	25 µg twice daily
10	25 µg twice daily	12.5 µg twice daily
11	25 µg once daily	50 µg once daily
12	50 µg once daily	25 µg once daily
13	12.5 µg twice daily	100 µg once daily
14	100 µg once daily	12.5 µg twice daily
15	25 µg once daily	50 µg twice daily
16	50 µg twice daily	25 µg once daily

(Source: Table 9-2 Treatment Sequences, Study NVA237A2208 report.)

Table 35. Dosing Regimen of Study NVA237A2208

Assigned Study Treatment	A.M. Dosing	P.M. Dosing
b.i.d. (irrespective of dose)	NVA237	NVA237
q.d. (irrespective of dose)	NVA237	placebo
placebo	placebo	placebo

(Source: Table 9-3 Dosing Regimen, Study NVA237A2208 report.)

Clinical Endpoints:

- The primary efficacy endpoint was trough FEV1 (calculated as the average of the 23h 15min and 23h 45min measurements).
- A key secondary efficacy endpoint was the maximum difference in mean response between BID and QD regimens.
- Important secondary analyses were based on standardized FEV1 AUC 0-24h on Days 1, 14 and 28.
- Other secondary endpoints included FEV1 AUC 0-4h, FEV1 AUC 0-8h, FEV1 AUC 0-12h and FEV1 AUC 12-24h, FEV1 at 12h, peak FEV1, FVC and weekly rescue medication use.
- Safety assessments.

Statistical Methods

The analysis of primary and secondary endpoints was performed using the full analysis set (FAS). The per-protocol (PP) set was used for supportive analysis of the primary endpoint only.

Non-linear mixed effects modeling was used to characterize the NVA237 total daily dose versus trough FEV1 relationship for QD and BID regimens in the primary variable analysis. Briefly, 8 candidate models based on the Emax dose-response shape were tried to describe the evolution of dose response over time. A model-averaging process was

then employed to obtain response predictions as the weighted average of individual model predictions and confidence limits derived using a simulation-based procedure. The estimated trough response at Day 28 was derived using the statistical models and the estimated Emax from each model was used to calculate the percentage of maximal effect as 100 × response/Emax.

In addition, ANCOVA model (as below) was used to analyze FEV_1 and FVC at each time point of each visit, and trough FEV_1 and FEV_1 AUC 0-24h at Day 28/29. The (period) baseline FEV_1 is defined as the mean of 2 values taken at 45 min and 15 min prior to study drug administration in the treatment period.

FEV_1 = patient effect + period effect + treatment effect + (period) baseline FEV_1 + baseline
ICS use + covariates + error

Efficacy Results:

Primary Efficacy Results
Dose response results of trough FEV1 for the model-averaged analysis at Day 28 are a shown in Figure 21, Figure 22, and Table 36.

Following 28-day treatment, all NVA237 treatment groups had statistically significant absolute increases in mean trough FEV1 compared to placebo. Within each treatment regimen there was a dose-related increase in trough FEV1. The treatment differences for all NVA237 doses compared to placebo ranged from 0.051L (27.1% Emax) for the 12.5 mcg QD treatment group, to 0.160 L (85.4% Emax) for 50 mcg BID. NVA237 12.5 mcg BID dose was the lowest dose with a clinically important difference (0.115 L, 61.6% Emax) compared to placebo.

When comparing the regimens, at Day 28, the BID regimen provided greater improvement in trough FEV_1 compared to placebo than the QD regimen for the total daily doses of 25, 50 mcg, and 100 mcg. For the 50 mcg QD dose the treatment difference compared to placebo was 0.109L (58.5% Emax), compared with 0.141L (75.5% Emax) for 25mcg BID and 0.115L (61.6% Emax) for 12.5 mcg BID The 100 mcg QD dose provided a small incremental benefit over the 50 mcg QD dose (0.027L). For the total daily doses of 25, 50 and 100 mcg, the differences between the QD and BID regimens were not clinically meaningful.

Similar results were observed at Days 7 and 14, meaning the treatment improvement could be achieved after 7 days of treatment.

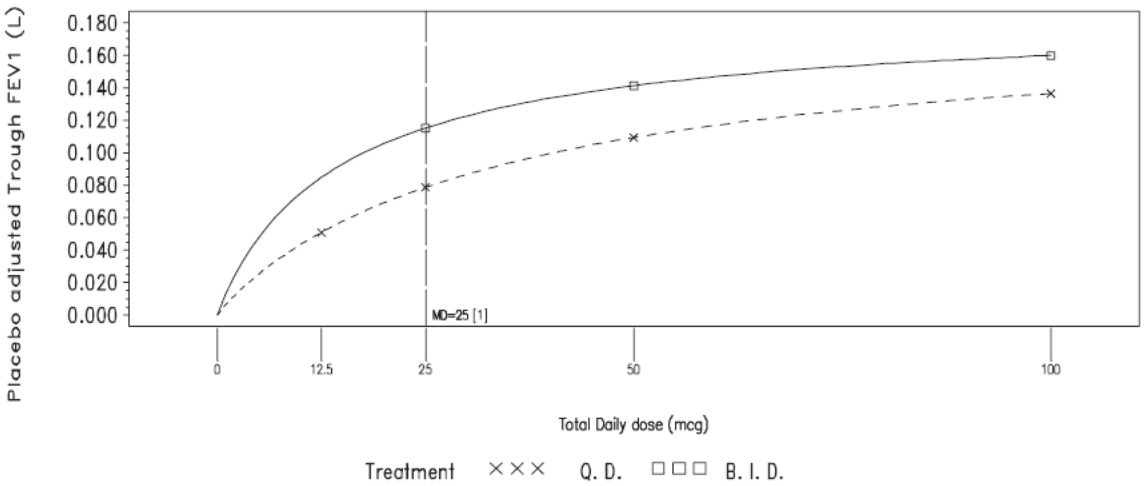


Figure 21. Dose response curves of trough FEV1 for Day 28 for model-averaged analysis by treatment regimen

MD = Maximum difference. This is indicated on the figure by a dashed vertical line.
[1] Among all the total daily doses between 20ug and 55ug in the increment of 5ug, this is the total daily dose which the BID regimen has the maximum numerical difference over the QD regimen.
(Source: Figure11-1, Study NVA237A2208 report.)

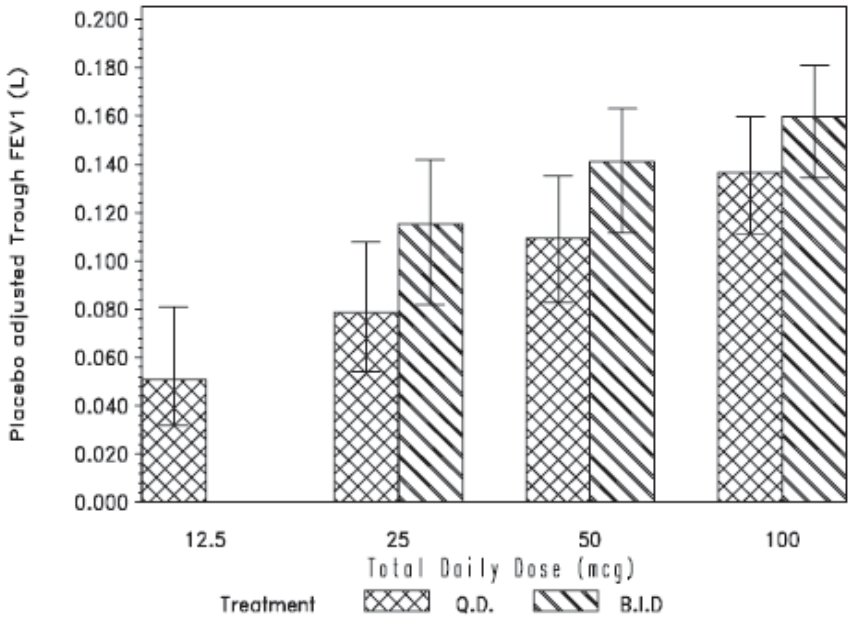


Figure 22. Trough FEV1 (L) (including 90% confidence limits) for Day 28 for model-averaged analysis by treatment regimen

Source: Figure11-2, Study NVA237A2208 report.

Table 36. Dose-response results of trough FEV1 (L) for model-averaged analysis by treatment at Day 28

Treatment	Absolute increase over Placebo (L)	SE	90% CI	Percentage of Projected Maximum Effect of any NVA237 dose	SE	90% CI
NVA237 12.5 µg q.d.	0.051	0.019	(0.032, 0.081)	27.1	10.5	(16.4, 44.3)
NVA237 25 µg q.d.	0.079	0.020	(0.054, 0.108)	42.0	11.8	(26.5, 61.4)
NVA237 12.5 µg b.i.d.	0.115	0.021	(0.082, 0.142)	61.6	13.9	(36.6, 82.1)
NVA237 50 µg q.d.	0.109	0.020	(0.083, 0.135)	58.5	12.0	(37.5, 76.2)
NVA237 25 µg b.i.d.	0.141	0.020	(0.112, 0.163)	75.5	12.6	(48.7, 90.2)
NVA237 100 µg q.d.	0.137	0.019	(0.111, 0.160)	73.0	11.5	(49.0, 86.5)
NVA237 50 µg b.i.d.	0.160	0.020	(0.135, 0.181)	85.4	11.2	(60.4, 94.8)

The period baseline FEV1 is the mean of the 45 and 15 minutes pre-dose FEV1 values at each period. Trough FEV1 was defined as the mean of the FEV1 values measured at 23 hours 15 mins and 23 hours 45 mins post-dose. Percentage of projected maximum effect of any NVA237 dose = (Effect of this NVA dose /maximum theoretical effect predicted by model) x 100%
(Source: Table11-7, Study NVA237A2208 report)

Secondary Efficacy Results

Key secondary efficacy results (The maximum difference in mean response between BID and QD regimens)

The differences between the two regimens were small and not clinically meaningful over the total daily dose range of 20 mcg to 55 mcg (Table 37). The greatest difference (0.037L) occurred between 12.5 mcg BID and 25 mcg QD.

Table 37. Difference in mean response of trough FEV1 (L) between dosing regimens over the range 20 mcg to 55 mcg total daily dose after 28 days of treatment

Total daily dose	Comparison	Treatment difference	90% CI
20 µg	10 µg b.i.d. - 20 µg q.d.	0.037	(0.013, 0.053)
25 µg	12.5 µg b.i.d. - 25 µg q.d.	0.037 [1]	(0.013, 0.052)
30 µg	15 µg b.i.d. - 30 µg q.d.	0.036	(0.013, 0.051)
35 µg	17.5 µg b.i.d. - 35 µg q.d.	0.035	(0.013, 0.050)
40 µg	20 µg b.i.d. - 40 µg q.d.	0.034	(0.013, 0.049)
45 µg	22.5 µg b.i.d. - 45 µg q.d.	0.033	(0.013, 0.047)
50 µg	25 µg b.i.d. - 50 µg q.d.	0.032	(0.012, 0.046)
55 µg	27.5 µg b.i.d. - 55 µg q.d.	0.031	(0.012, 0.045)

(Source: Table11-8, Study NVA237A2208 report)

Important secondary efficacy results

AUC0-24h FEV1 after 28 days of treatment
Within each treatment regimen, the AUC0-24h FEV1 increased with dose. The treatment differences compared with placebo ranged from 0.058 L (28.9% Emax) for 12.5 mcg BID group to 0.158 L (79.3% Emax) for 50 mcg BID group. There was no statistical significant difference in AUC0-24h FEV1 between QD and BID dose regiment with the

total daily doses of 25, 50 and 100 mcg (Figure 23, Table 38). Similar results were observed for AUC0-24 h FEV1 over the 28 days of treatment.

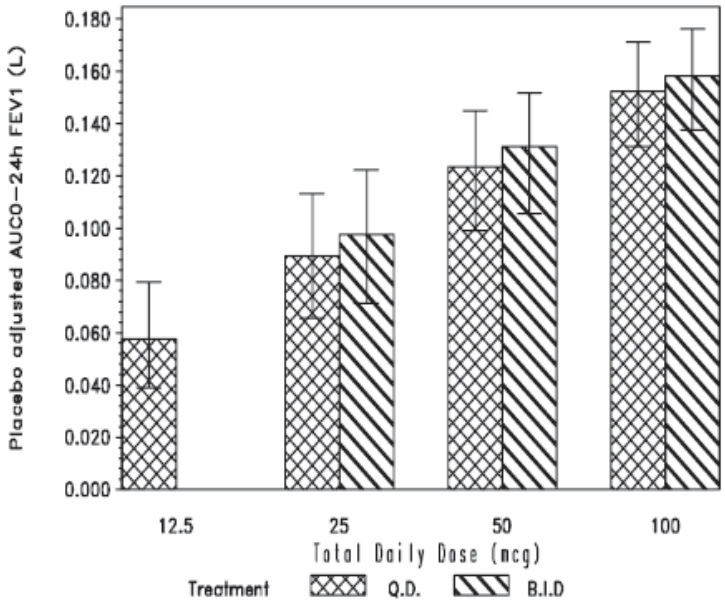


Figure 23. FEV1 AUC0-24h for Day 28 for model-averaged analysis by treatment regimen
(Source: Figure 11-3, Study NVA237A2208 report)

Table 38. Dose-response results of FEV1 AUC0-24h for model-averaged analysis by treatment at Day 28

Treatment	Absolute increase over Placebo (L)	SE	90% CI	Percentage of Projected Maximum Effect of any NVA237 dose	SE	90% CI
NVA237 12.5 µg q.d.	0.058	0.012	(0.039, 0.079)	28.9	7.0	(18.7, 41.6)
NVA237 25 µg q.d.	0.089	0.014	(0.066, 0.113)	44.8	8.2	(31.6, 58.8)
NVA237 12.5 µg b.i.d.	0.098	0.015	(0.071, 0.122)	49.0	9.1	(34.1, 64.1)
NVA237 50 µg q.d.	0.123	0.014	(0.099, 0.145)	61.9	7.9	(48.0, 74.0)
NVA237 25 µg b.i.d.	0.131	0.014	(0.106, 0.152)	65.7	8.3	(50.9, 78.1)
NVA237 100 µg q.d.	0.152	0.012	(0.131, 0.171)	76.4	6.2	(64.8, 85.1)
NVA237 50 µg b.i.d.	0.158	0.012	(0.138, 0.176)	79.3	6.2	(67.5, 87.7)

(Source: Table11-9, Study NVA237A2208 report)

Sponsor also evaluated the maximum difference in mean response of AUC0-24h FEV1 between QD and b.i.d regimen over the total daily dose range of 20 mcg and 55 mcg. Results indicated the treatment difference between two regimens was not clinically meaningful. (Figure 24 and Table 39)

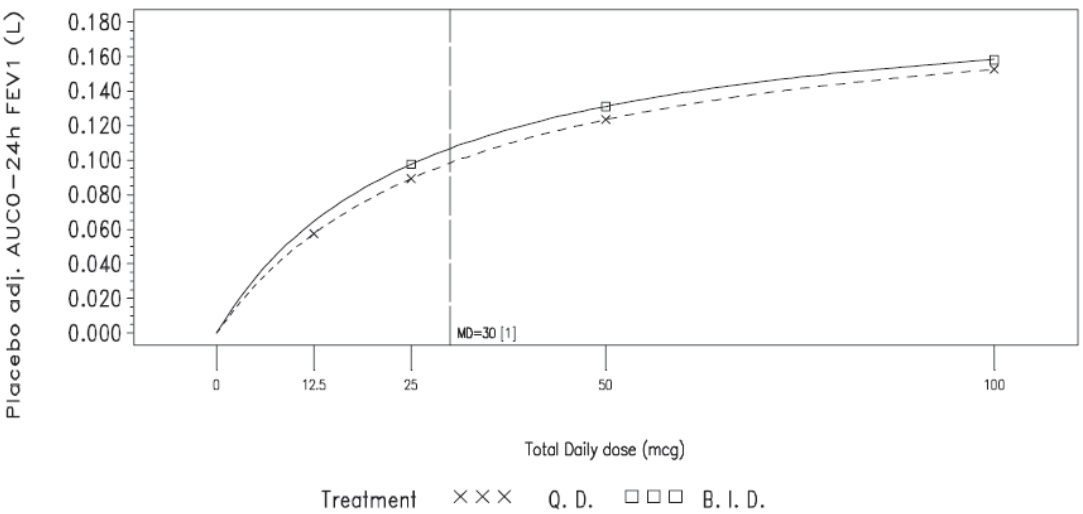


Figure 24. Dose response curves of FEV1 AUC0-24h for Day 28 for model averaged analysis by treatment regimen

Source: Figure 11-4, Study NVA237A2208 report.

Table 39. Difference in mean response of FEV1 AUC0-24h between dosing regimens over the range 20 mcg to 55 mcg total daily dose after 28 days of treatment

Total daily dose	Comparison	Treatment difference	90% CI
20 µg	10 µg b.i.d. - 20 µg q.d.	0.008	(-0.008, 0.023)
25 µg	12.5 µg b.i.d. - 25 µg q.d.	0.008	(-0.008, 0.024)
30 µg	15 µg b.i.d. - 30 µg q.d.	0.008 [1]	(-0.008, 0.024)
35 µg	17.5 µg b.i.d. - 35 µg q.d.	0.008	(-0.008, 0.023)
40 µg	20 µg b.i.d. - 40 µg q.d.	0.008	(-0.008, 0.023)
45 µg	22.5 µg b.i.d. - 45 µg q.d.	0.008	(-0.008, 0.022)
50 µg	25 µg b.i.d. - 50 µg q.d.	0.008	(-0.008, 0.022)
55 µg	27.5 µg b.i.d. - 55 µg q.d.	0.007	(-0.007, 0.021)

Source: Table11-10, Study NVA237A2208 report.

Other secondary efficacy results

For other secondary efficacy endpoints including AUC0-4h FEV1, AUC0-8h FEV1, AUC0-12h FEV1, AUC0-12h FEV1, AUC12-24h FEV1, FEV1 at 12 h, and peak FEV1, a dose-related increase was observed within each treatment regimen after 28 days of treatment. There was no statistical significant difference in each of them between QD and BID dose regimen with the total daily doses of 25, 50 and 100 mcg. Similar results were observed at Days 7 and 14, meaning the treatment improvement could be achieved after 7 days of treatment.

Safety Results:

Overall, there was no regimen or dose related AEs incidence. All NVA237 dose regimens had lower AEs incidence compared with placebo.

Conclusions:

Efficacy

Primary Efficacy endpoint

Following 28-day treatment, all NVA237 treatment groups had statistically significant absolute increases in mean trough FEV1 compared to placebo. Within each treatment regimen there was a dose-related increase in trough FEV1. NVA237 12.5 mcg BID dose was the lowest dose with a clinically important difference (0.115 L) compared to placebo.

When comparing the regimens, at Day 28, the BID regimen provided greater improvement in trough FEV_1 compared to placebo than the QD regimen for the total daily doses of 25, 50, and 100 mcg. For the total daily doses of 25, 50, and 100 mcg, the differences between QD and BID regimens were not clinically meaningful.

Similar results were observed at Days 7 and 14, meaning the treatment improvement could be achieved after 7 days of treatment.

Secondary Efficacy endpoint

Key secondary efficacy (The maximum difference in mean response between BID and QD regimens): The treatment differences between QD and BID regimens were small and not clinically meaningful over the total daily dose range of 20 mcg to 55 mcg. The greatest difference (0.037L) occurred between 12.5 mcg BID and 25 mcg QD.

Important secondary efficacy **(**AUC0-24h FEV1 after 28 days of treatment): Within each treatment regimen, the AUC0-24h FEV1 increased with dose. There was no statistical significant difference in AUC0-24h FEV1 between QD and BID dose regiment with the total daily doses of 25, 50 and 100 mcg. Similar results were observed for AUC0-24 h FEV1 over the 28 days of treatment.

Other secondary efficacy **(**AUC0-4h FEV1, AUC0-8h FEV1, AUC0-12h FEV1, AUC0-12h FEV1, AUC12-24h FEV1, FEV1 at 12 h, and peak FEV1 after 28 days of treatment): a dose-related increase was observed within each treatment regimen after 28 days of treatment. There was no statistical significant difference between QD and BID dose regimen with the total daily doses of 25, 50 and 100 mcg. The treatment improvement could be achieved after 7 days of treatment.

Safety

Overall, there was no regimen or dose related AEs incidence. All NVA237 dose regimens were safe and well tolerated.

For further details regarding efficacy and safety, refer to the Clinical Review for NDA207923.

Phase 3 Efficacy and Safety Study in COPD Patients

Study CNVA237A2317

Title: A 12-week multi-center, randomized, double-blind, placebo controlled study to assess the efficacy and safety of NVA237 in stable COPD patients

Objectives:

Primary: to demonstrate superiority of NVA237 12.5 mcg BID versus placebo with respect to FEV1 between 0 - 12 h post dosing (FEV1 AUC 0-12h) at Week 12 of treatment in COPD patients with moderate or severe airflow limitation.

Secondary: to evaluate the efficacy, safety and tolerability of NVA237 12.5 mcg BID

Study Design and Treatment Schedule:
This study used a multi-center, double-blind, placebo-controlled, parallel-group, randomized design to evaluate the efficacy and safety of NVA237 12.5 mcg BID in COPD patients with moderate to severe airflow limitation. Study treatments were given in addition to permitted COPD background therapy with inhaled corticosteroids (ICS).

The two treatment arms (1:1) are:

- NVA237 12.5 mcg BID, Concept 1
- Placebo BID, Concept 1

The study consisted of a screening epoch (length was dependent on washout required for prior medications between 7 to 1 days), a 14-day run-in epoch, a baseline/randomization visit (occurred on the same day), and a 12 week treatment epoch (NVA237 12.5 mcg BID or placebo), followed by a study completion evaluation and a follow-up epoch of 30 days. The study design was shown as below (Figure 25).

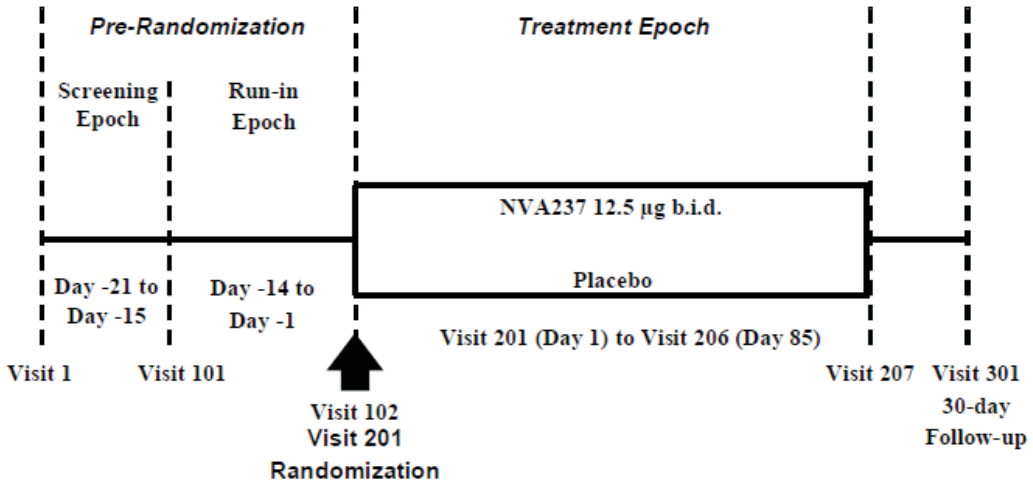


Figure 25. Study design
(Source: Figure 9-1, Study CNVA237A2317 report)

PK Sampling Schedule

Blood samples for PK and pharmacogenomics analyses were collected from consenting patients pre-dose, and at 2 min, 20 min, 55 min, 3.5 h, and 5 h postdose on Days 29 and 85.

The PK data was pooled with PK data from other studies and analyzed using a population approach. Results were reported separately.

Results

Efficacy Results

The primary efficacy results (FEV1 AUC0-12h at Week 12) were shown in the Table as below. After 12 weeks of treatment, the least squares (LS) mean treatment difference for change from baseline in FEV1 AUC(0-12h) was 0.139 L for NVA237 vs placebo in the FAS, which was statistically significant ($p<0.001$) and clinically meaningful. Please refer Clinical Review for more detail regarding efficacy results.

Table 40. Mixed model for repeated measures (MMRM) of change from baseline in FEV1 (L) AUC(0-12h) at Week 12 (FAS)

Number of patients included in the analysis - NVA 12.5 bid: n = 222, Pbo: n = 216					
	CFB in FEV_1 AUC		---------- Treatment difference ----------		
Treatment	LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
NVA237	0.125 (0.0162)	NVA 12.5 bid - Pbo	0.139 (0.0225)	(0.095, 0.184)	<0.001
Pbo	-0.014 (0.0165)				

MMRM: change from baseline in FEV_1 AUC = treatment + baseline FEV_1 + smoking status at baseline + baseline ICS use + visit (Days 1 and 85) + treatment * visit interaction + baseline FEV_1 * visit interaction.
Baseline FEV_1 was defined as the average of the -45 min and -15 min FEV_1 values taken on Day 1.

(Source: Table 11-6, Study CNVA237A2317 report)

PK Results

The PK data was pooled with PK data from other studies and analyzed using a population approach. Results were not reported in this study report.

Conclusions

NVA237 12.5 mcg BID demonstrated statistically significant and clinically meaningful improvements in lung function on Day 1 and sustained up to Week 12. NVA237 12.5 mcg BID regimen was safe and well tolerated with a safety profile similar to placebo.

For further details regarding efficacy and safety, refer to the Clinical Review for NDA207923.

Efficacy and Safety Study in COPD Patients

Study CNVA237A2318

Title: A 12-week multi-center, randomized, double-blind, placebo controlled study to assess the efficacy and safety of NVA237 in stable COPD patients

Objectives

Primary: to demonstrate superiority of NVA237 12.5 mcg BID versus placebo with respect to FEV1 AUC 0-12h at Week 12 of treatment in COPD patients with moderate or severe airflow limitation.

Secondary: to evaluate the efficacy, safety, and tolerability of NVA237 12.5 mcg BID

Study Design and Treatment Schedule:
This study used a multi-center, double-blind, placebo controlled, parallel-group, randomized design (1:1) to evaluate the efficacy and safety of NVA237 12.5 mcg BID in COPD patients with moderate to severe airflow limitation. Study treatments were given in addition to permitted COPD background therapy (Figure 26).

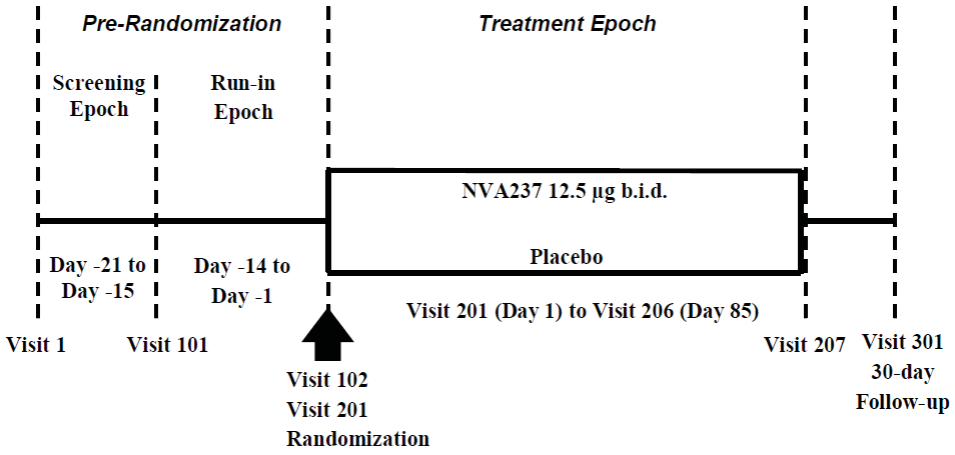


Figure 26. Study design
(Source: Figure 9-1, Study NVA237A2318 report)

NVA237 and matching placebo were provided as powder filled capsules (HPMC capsules, size III), packaged in blisters, together with a SDDPI.

Table 40. Test Product

Treatment	Strength	Batch #
NVA235, 12.5mcg, BID	12.5mcg	X098EI
Placebo, BID	NA	X124CH
Inhalers (SDDPIs) for NVA 12.5 mcg & Placebo	NA	B0970B011001

Efficacy Assessment
All patients performed spirometry in the clinic at every treatment epoch visit. All patients performed 12 hour serial spirometry assessments at Visit 201 (Day 1) and Visit 206 (Day 85), as well as trough FEV1 assessments on the following days at 23:15 h and 23:45 h post the morning dose (named Visit 202 on Day 2 and Visit 207 on Day 86). These time

points at Visits 202 and 207 corresponded to 11:15 h and 11:45 h, respectively, post the last evening dose. All patients were required to remain at the clinic for the 12 hour period on Days 1 and 85, and returned to the clinic in the morning of the next day (Days 2 and 86) for the trough FEV1 assessments. SGRQ, CAT and BDI/TDI were assessed in all patients at Visit 201 (Day1) and Visit 206 (Day 85).

PK Sampling Schedule
PK (blood) sampling was performed in a subset of patients only.
Days 29 and 85: pre-dose, 2min, 20 min, 55 min, 3.5h, and 5h pose-dose.

Results
A total of 1144 patients were screened of whom 432 were randomized to either NVA237 12.5 mcg BID or placebo. Approximately 90% of patients completed the study.

Efficacy results
Primary efficacy results (FEV1 AUC(0-12h) at Week 12, overall): After 12 weeks of treatment, the least squares (LS) mean change from baseline in FEV1 AUC0-12h was 0.123 L for NVA237 vs. placebo in the FAS, which was statistically significant ($p<0.001$) and clinically meaningful (Table 41). Results of the sensitivity analyses in FAS AND PPS were consistent with the primary analysis.

Table 41. MMRM of change from baseline in FEV1 (L) AUC (0-12h) at Week 12

Number of patients included in the analysis - NVA 12.5 bid: n = 215, Pbo: n = 213					
			---------- Treatment difference ----------		
Treatment	CFB in FEV_1 AUC LS Mean (SE)	Comparison	LS Mean (SE)	(95% CI)	p-value
NVA 12.5 bid	0.115 (0.0153)	NVA 12.5 bid - Pbo	0.123 (0.0213)	(0.081, 0.165)	<0.001
Pbo	-0.008 (0.0153)				

Pbo=placebo
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from baseline.
MMRM: change from baseline in FEV_1 AUC = treatment + baseline FEV_1 + smoking status at baseline + baseline ICS use + visit (Days 1 and 85) + treatment*visit interaction + baseline FEV1*visit interaction.
Baseline FEV_1 is defined as the average of the -45 min and -15 min FEV_1 values taken on Day 1.
(Source: Table 11-6, Study NVA237A2318 report)

PK results
The PK data was pooled with PK data from other studies and analyzed by a population approach. The results of this analysis are reported separately from this CSR.

Conclusions
- NVA237 12.5 mcg BID demonstrated statistically significant and clinically meaningful improvements in lung function which were evident on Day 1 and sustained up to Week 12.
- NVA237 12.5 mcg administered twice daily was safe and well tolerated.

For further details regarding efficacy and safety, refer to the Clinical Review for NDA207923.

4.3. Appendix – New Drug Application Filing and Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	207923	**SDN**	
Applicant	Novartis	**Submission Date**	12/29/2014
Generic Name	Glycopyrrolate	**Brand Name**	SEEBRI™ NEOHALER
Drug Class	Long-acting muscarinic antagonist		
Indication	Chronic obstructive Pulmonary Disease		
Dosage Regimen	12.5 mcg, 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	☑ Standard ✗ Priority ✗ 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?
☑ Yes
✗ No
If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?
✗ Yes
☑ No
If yes list comment(s)

Is there a need for clinical trial(s) inspection?
✗ Yes
☑ No
If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ✗ No	Clinical Pharmacology Summary	☑ Yes ✗ No
Bioanalytical and Analytical Methods	☑ Yes ✗ No	Labeling	☑ Yes ✗ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☑ Metabolism Characterization	2	DMPK R0600683, DMPK R1100757,

☑ Transporter Characterization		3	DMPK R0800473, DMPK R0800758, DMPK R0900807,
☑ Distribution		2	DMPK R0800705, DMPK R1000635
☑ Drug-Drug Interaction		6	DMPK R0600082, DMPK R0800472, DMPK R0800502, DMPK R1000619, DMPK R1200048, DMPK R1200049
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability		1	CNVA237A2108
✗ Relative Bioavailability			
✗ Bioequivalence			
✗ Food Effect			
✗ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	CQVA149A2101
	☑ Multiple Dose	3	CQVA149A2103, CQVA149A2106, CQVA149A2107
Patients	✗ Single Dose		
	☑ Multiple Dose	1	NVA237A2103
✗ Mass Balance Study			
✗ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		2	NVA237A2104, CNVA237A2107
✗ Sex			
✗ Geriatrics			
✗ Pediatrics			
✗ Hepatic Impairment			
☑ Renal Impairment		1	CNVA237A2105
✗ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug		1	CNVA237A2109
✗ Effects of Primary Drug			
Pharmacodynamics			
✗ Healthy Subjects			
✗ Patients			
Pharmacokinetics/Pharmacodynamics			
☑ Healthy Subjects		1	CQVA149A2105
☑ Patients		4	CNVA237A2317, NVA237A2303, CNVA237A2304, NVA237A2309
☑ QT		1	CNVA237A2110
Pharmacometrics			
☑ Population Pharmacokinetics		4	NVA237 PopPK modeling low dose NVA237 PopPK modeling, NVA237 renal-impairment simulation NVA237 renal impairment Modeling NVA237 PopPK simulation J-NDA
✗ Exposure-Efficacy			

✗ Exposure-Safety					
Total Number of Studies					
Total Number of Studies to be Reviewed		**In Vitro**	13	**In Vivo**	20

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?	✗ Yes ✗ No ☑N/A	The to-be-marketed product was used in the pivotal clinical trials.
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3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ✗ No ✗ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	✗ Yes ✗ No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ✗ No ✗ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ✗ No ✗ 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)?	☑Yes ✗ No ✗ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ✗ No ✗ 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	☑Yes ✗ No ✗ 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?	☑Yes ✗No ✗N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
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1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ✗No ✗N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	✗Yes ✗No ☑N/A	
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3. Is the appropriate pharmacokinetic information submitted?	☑Yes ✗No ✗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)?	☑Yes ✗No ✗N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	✗Yes ✗No ☑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?	☑Yes ✗No ✗N/A	

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

Filing Memo
This is optional, discuss with your TL content and format

Regulatory History

NVA237 (glycopyrrolate) has been in clinical use for indications other than COPD for over 40 years and has been approved in more than 70 countries. Some of the products in current US market are shown in the following table.

Table 1. Approved glycopyrrolate drug products in the US*

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 to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. 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 with neurologic conditions associated with problem drooling (e.g., cerebral palsy).

*Approved glycopyrrolate generic drug products are not listed.

Novartis initiated the development of NVA237 for treatment of COPD by investigating (b) (4) . In IND48655 (NVA237) end-of-Phase 2 meeting (July 15, 2008) and pre-NDA meeting (September 28, 2011), FDA disagreed the proposed dosing regimen and recommended to evaluate more frequent dosing intervals (b) (4) .

In the Type C meeting request dated September 23, 2013, Novartis updated that Phase 3 studies are in process to access the safety and efficacy of NVA237 12.5 mcg BID, which was selected as the NVA237 dosing regimen to support the US FDA submission under NDA 207923.

Clinical Pharmacology Studies

The relevant clinical pharmacology studies submitted under NDA 207923 were summarized in Table 2.

Table 2. Summary of Relevant Clinical Pharmacology Studies

	Study ID	Study Design	Objectives	Treatments
BA study in HV	CNVA237A2108	OL, R, partly DB, crossover, SD, N=10 (part1) /20(part2)	Absolute BA, PK, PD, Safety	Part1: oral NVA 400 mcg w/o or w/ activated charcoal Part 2 : IV glycopyrrolate 120 mcg or placebo; inhaled NVA 200 mcg w/o or w/ oral activated charcoal
PK study in HV	CQVA149A2101	OL, R, crossover, SD, N=28	Safety, PK	QAB 300 mcg, Concept 1 NVA 100 mcg, Concept 1 QVA 300/100 mcg, Concept 1
	CQVA149A2103	OL, R, crossover, MD, N=42	Safety, PK	Concept 1 device QAB 150 mcg, QD, Concept 1 NVA 50 mcg, QD, Concept 1 QVA 150/50 mcg, QD, Concept1
	CQVA149A2106	OL, R, crossover, MD, N=24	Safety, PK	Concept 1 device QAB 150 mcg, QD, Concept 1 NVA 50 mcg, QD, Concept 1 QVA 150/50 mcg,QD,Concept1
	CQVA149A2107	OL, R, crossover, MD, N=36	PK, Safety	QAB 27.5 mcg×2, BID NVA 12.5mcg ×2, BID QAB 75 mcg×2, QD QVA 27.5/12.5 mcg×2, BID
PK study in COPD patient	NVA237A2103	R, DB, parallel-group, MD, N=41	PD, PK, Safety	NVA 25 mcg, QD, Concept 1 NVA 50 mcg, QD, Concept 1 NVA 100 mcg, QD, Concept 1 NVA 200 mcg, QD, Concept 1 Placebo, QD, Concept 1
Intrinsic factor study	NVA237A2104	R, DB, crossover, SD, in Caucasian and Japanese, N=37	PK, Safety	NVA 50 mcg, Concept 1 NVA 100 mcg , Concept 1 NVA 200 mcg, Concept 1
	CNVA237A2105	OL, non-R, parallel-group, SD, N=48	Impact of renal impairment, PK, Safety	NVA 100 mcg, Concept 1
	CNVA237A2107	OL, MD, in Chinese, N=12	PK and safety	NVA 50 mcg, QD, Concept 1
Extrinsic factor study	CNVA237A2109	R, OL, crossover, SD, N=20	Impact of co-administration of cimetidine, PK, Safety	NVA 100 mcg, SD, Concept 1 Cimetidine, oral, 800 mg× 6 days

PD and PK/PD study in HV	CNVA237A2110	R, partially-blinded, crossover, placebo and positive controlled, SD, N=73	PK/PD, Safety	NVA 400 mcg, SD, Concept 1 Moxifloxacin, SD, oral,400mg Placebo
	CQVA149A2105	DB, R, placebo and active controlled, incomplete crossover, N=50	PD, Safety, PK	QVA 440/200 mcg, Concept 1 QAB 600 mcg, Concept 1 NVA 200 mcg, Concept 1 Salmeterol 200 mcg, Concept 1 Placebo
Efficacy and safety study	NVA237A2208	R, DB, placebo-controlled, crossover, N=386	Dose-ranging, Efficacy, Safety	NVA 12.5 mcg, QD, Concept 1 NVA 25 mcg, QD, Concept 1 NVA 12.5 mcg, BID, Concept 1 NVA 50 mcg, QD, Concept 1 NVA 25 mcg, BID, Concept 1 NVA 100 mcg, QD, Concept 1 NVA 50 mcg, BID, Concept 1 Placebo
	CNVA237A2317	R, DB, placebo controlled, 12-week treatment, N=441	Safety, Efficacy, PK, PG	NVA 12.5 mcg, BID, Concept 1 Placebo
	NVA237A2303	R, DB, placebo-controlled, parallel group, 52-week treatment, N=1060	Efficacy, Safety, PK	NVA 50mcg, QD, SDDPI Placebo Tiotropium, 18 mcg, QD, Hadihaler
	CNVA237A2304	R, DB, placebo-controlled, parallel, 26-week treatment, N=817	Efficacy, Safety, PK	NVA 50 mcg, QD, SDDPI Placebo
	NVA237A2309	R, DB, placebo-controlled, parallel, 26-week treatment, N=459	Efficacy, Safety, PK	NVA 50 mcg, QD, SDDPI Placebo

*BA: bioavailability; HV: healthy volunteers; 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

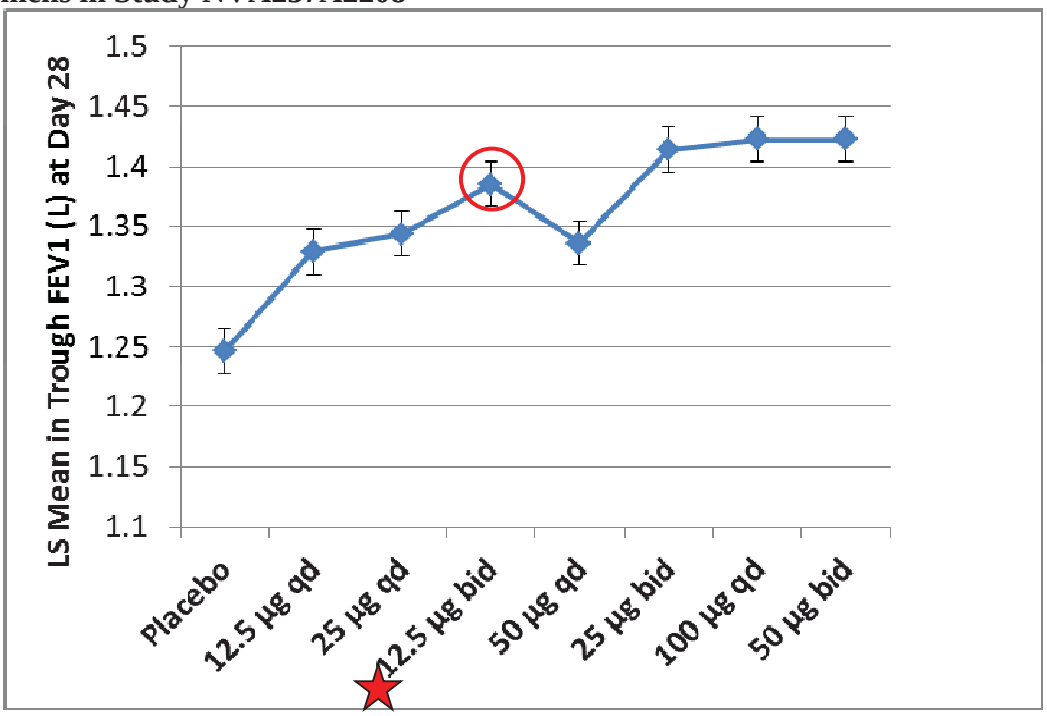
Dose and Dose Regimen Selection

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 12.5 mcg QD, 25 mcg QD, 50 mcg QD, and 100 mcg QD. The treatment difference (NVA237 vs. placebo) for trough FEV1 on Day 7 were dose-ordered, ranging from 0.075 L (12.5 mcg QD) to 0.142 L (100 mcg 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 dosing regimens included NVA237 12.5 mcg QD, 25 mcg QD, 12.5 mcg BID, 50 mcg QD, 25 mcg BID, 100 mcg QD, and 50 mcg BID. According to the data analysis, on Day 28, all NVA237 doses had a significant higher mean trough FEV1 when compared to placebo. NVA237 12.5 mcg 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 doing regiment to support the submission under NDA207923 (Figure 1).

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



Summary of NVA237 PK

The PK characteristics of NVA237 are summarized in Table 3. Following oral inhalation from the NVA237 inhalation powder hard capsules via the Concept 1 device, the absolute bioavailability of glycopyrrolate is 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.

Table 3. PK Characteristics of NVA237 (Glycopyrrolate)

	NVA237 (Glycopyrrolate)
Tmax	5 min
Bioavailability	40%
Protein binding	Plasma: 38-41%
T1/2	33-57 hrs
Linear PK	50 - 200 µg
Metabolism	Minor
Elimination	Renal 60-70%, Non-renal 30-40% Mostly parent
Food effect	Minimal

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	207923	**SDN**	
Applicant	Novartis	**Submission Date**	12/29/2014
Generic Name	Glycopyrrolate	**Brand Name**	SEEBRI™ NEOHALER
Drug Class	Long-acting muscarinic antagonist		
Indication	Chronic obstructive Pulmonary Disease		
Dosage Regimen	12.5 µg, 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	☑ Standard ☐ Priority ☐ 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?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☑ Metabolism Characterization	2	DMPK R0600683, DMPK R1100757,
☑ Transporter Characterization	3	DMPK R0800473, DMPK R0800758, DMPK R0900807,
☑ Distribution	2	DMPK R0800705, DMPK R1000635
☑ Drug-Drug Interaction	6	DMPK R0600082, DMPK R0800472, DMPK R0800502, DMPK R1000619, DMPK R1200048, DMPK R1200049
In Vivo Studies		

Biopharmaceutics			
☑ Absolute Bioavailability		1	CNVA237A2108
☐ Relative Bioavailability			
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☐ Food Effect			
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Healthy Subjects	☑ Single Dose	1	CQVA149A2101
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☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		2	NVA237A2104, CNVA237A2107
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☑ Renal Impairment		1	CNVA237A2105
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Total Number of Studies	**In Vitro**		**In Vivo**	
Total Number of Studies to be Reviewed		13		20

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RTF Parameter	**Assessment**	**Comments**
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	CQVA149A2103	OL, R, crossover, MD, N=42	Safety, PK	Concept 1 device QAB 150 µg, QD, Concept 1 NVA 50 µg, QD, Concept 1 QVA 150/50 µg, QD, Concept1
	CQVA149A2106	OL, R, crossover, MD, N=24	Safety, PK	Concept 1 device QAB 150 µg, QD, Concept 1 NVA 50 µg, QD, Concept 1 QVA 150/50 µg,QD,Concept1
	CQVA149A2107	OL, R, crossover, MD, N=36	PK, Safety	QAB 27.5 µg×2, BID NVA 12.5µg ×2, BID QAB 75 µg×2, QD QVA 27.5/12.5 µg×2, BID
PK study in COPD patient	NVA237A2103	R, DB, parallel-group, MD, N=41	PD, PK, Safety	NVA 25 µg, QD, Concept 1 NVA 50 µg, QD, Concept 1 NVA 100 µg, QD, Concept 1 NVA 200 µg, QD, Concept 1 Placebo, QD, Concept 1
Intrinsic factor study	NVA237A2104	R, DB, crossover, SD, in Caucasian and Japanese, N=37	PK, Safety	NVA 50 µg, Concept 1 NVA 100 µg , Concept 1 NVA 200 µg, Concept 1
	CNVA237A2105	OL, non-R, parallel-group, SD, N=48	Impact of renal impairment, PK, Safety	NVA 100 µg, Concept 1

	CNVA237A2107	OL, MD, in Chinese, N=12	PK and safety	NVA 50 µg, QD, Concept 1
Extrinsic factor study	CNVA237A2109	R, OL, crossover, SD, N=20	Impact of co-administration of cimetidine, PK, Safety	NVA 100 µg, SD, Concept 1 Cimetidine, oral, 800 mg× 6 days
PD and PK/PD study in HV	CNVA237A2110	R, partially-blinded, crossover, placebo and positive controlled, SD, N=73	PK/PD, Safety	NVA 400 µg, SD, Concept 1 Moxifloxacin, SD, oral,400mg Placebo
	CQVA149A2105	DB, R, placebo and active controlled, incomplete crossover, N=50	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
Efficacy and safety study	NVA237A2208	R, DB, placebo-controlled, crossover, N=386	Dose-ranging, Efficacy, Safety	NVA 12.5 µg, QD, Concept 1 NVA 25 µg, QD, Concept 1 NVA 12.5 µg, BID, Concept 1 NVA 50 µg, QD, Concept 1 NVA 25 µg, BID, Concept 1 NVA 100 µg, QD, Concept 1 NVA 50 µg, BID, Concept 1 Placebo
	CNVA237A2317	R, DB, placebo controlled, 12-week treatment, N=441	Safety, Efficacy, PK, PG	NVA 12.5 µg, BID, Concept 1 Placebo
	NVA237A2303	R, DB, placebo-controlled, parallel group, 52-week treatment, N=1060	Efficacy, Safety, PK	NVA 50µg, QD, SDDPI Placebo Tiotropium, 18 µg, QD, Hadihaler
	CNVA237A2304	R, DB, placebo-controlled, parallel, 26-week treatment, N=817	Efficacy, Safety, PK	NVA 50 µg, QD, SDDPI Placebo
	NVA237A2309	R, DB, placebo-controlled, parallel, 26-week treatment, N=459	Efficacy, Safety, PK	NVA 50 µg, QD, SDDPI Placebo

*BA: bioavailability; HV: healthy volunteers; 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

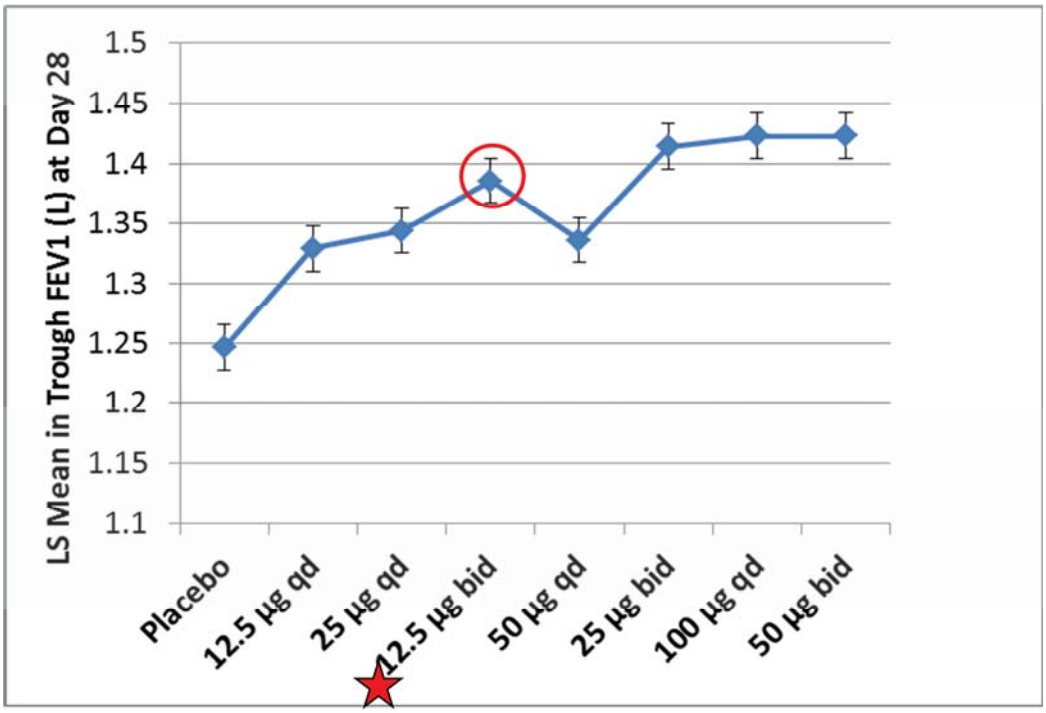
Dose and Dose Regimen Selection

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 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 a 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 submission under NDA207923 (Figure 1).

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



Summary of NVA237 PK

The PK characteristics of NVA237 are summarized in Table 3. Following oral inhalation from the NVA237 inhalation powder hard capsules via the Concept 1 device, the absolute bioavailability of glycopyrrolate is 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.

Table 3. PK Characteristics of NVA237 (Glycopyrrolate)

	NVA237 (Glycopyrrolate)
Tmax	5 min
Bioavailability	40%
Protein binding	Plasma: 38-41%
T1/2	33-57 hrs
Linear PK	50 - 200 μg
Metabolism	Minor
Elimination	Renal 60-70%, Non-renal 30-40% Mostly parent
Food effect	Minimal

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02/24/2015

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