1 August 2012
EMA/CHMP/508029/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Seebri Breezhaler

International non-proprietary name: **glycopyrronium bromide**

Procedure No.: **EMEA/H/C/002430**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Table of contents

List of abbreviations

ABC	ATP-binding cassette
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
b.i.d.	Bis in diem/twice daily
BDI	Baseline dyspnea index
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CCV	Cardio- and cerebro-vascular
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
Cmax	Maximum peak concentration
Cmax,ss	Maximum plasma concentration at steady-state
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CTD	Common Technical Document
CV	Cardiovascular
CYP	Cytochrome
DBP	Diastolic blood pressure
DRF	Dose-range finding
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMEA/EMA	European Medicines Evaluation Agency
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FMO	Flavin-containing monooxygenase enzyme
FVC	Forced vital capacity
GD	Gestation day
GI	Gastro-intestinal
GLP	Good laboratory practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	Glycopyrronium bromide
hERG	human ether-a-go-go-related gene
HPLC	High performance liquid chromatography
HR	Heart rate
HLT	High level term
IC	Inspiratory capacity
IC50	Inhibitor concentration producing 50% inhibition of enzyme or transporter activity
ICS	Inhaled corticosteroid
IT	Intratracheal
i.v.	Intravenous
Ki	Inhibitor binding constant
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic-antagonist
LC-MS	Liquid chromatography coupled with mass spectrometry
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LOQ	Limit of quantification
LOAEL	Lowest observed adverse effect level
LS	Least square means
MACE	Major adverse cardiovascular event
MAP	Mean arterial blood pressure

MATE1	Multi-drug and toxin extrusion protein
MCID	Minimal clinically important difference
MDR	Multidrug-resistant protein efflux transporter
MedDRA	Medical Dictionary for Regulatory Affairs
MMAD	Mass median aerodynamic diameter
MRP	Multidrug resistance-associated protein efflux transporter
MS	Mass spectrometry
MXR	Breast cancer resistant protein or mitoxantrone resistant protein efflux transporter
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NVA/NVA237	glycopyrronium bromide
OCT	Organic cation transporter
o.d.	omnie die/every day
OL	Open label
OR	Odds ratio
Pbo	Placebo
PD	Pharmacodynamic(s)
PEC	Predicted environmental concentration
Ph.Eur	European Pharmacopoeia
PK	Pharmacokinetic(s)
pKi	Apparent binding affinity constant
PO	Oral
PY	Patient-years
QBA608	([3S,2R]-threo-isomer) of NVA237
QBA609	([3R,2S]-threo-isomer) of NVA 237
q.d.	quaque die/every day
QTcF	QTc (Fridericia correction)
RI	Renal impairment
RTI	Respiratory tract infection
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SDDPI	Single dose dry powder inhaler
SLC	Solute carrier uptake transporters
SMQ	Standardized MedDRA query
SOC	System organ class
SGRQ	St Gorge Respiratory Questionnaire
SMETT	Sub-max constant-load cycle ergometry test
ss	Steady state
T½	Apparent elimination half-life
TDI	Transition dyspnea index
Tg	Transgenic
Tmax	Time to reach maximum concentration
Tio	Tiotropium
ULN	Upper limit normal
URTI	Upper respiratory tract infection
V	Volume of distribution
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 1 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Seebri Breezhaler, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2010. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: Seebri Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/4/2008 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Jens Heisterberg** Co-Rapporteur: **David Lyons**

- The application was received by the EMA on 1 September 2011.

- The procedure started on 21 September 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 December 2011.
- During the meeting on 16 - 19 January 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 January 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 May 2012.
- During the CHMP meeting on 21 – 24 May 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 31 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 June 2012.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Seebri Breezhaler on 21 June 2012.
- On 10 July 2012 the European Commission sent a letter to the CHMP Chairman requesting the CHMP to adapt the SmPC to the findings of the assessment report.
- The CHMP provided the requested clarifications in the revised SmPC adopted via written procedure on 1 August 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic obstructive pulmonary disease (COPD) is an illness characterized by air flow limitation that is not fully reversible. It is usually progressive and is associated with pathological changes in the lung - a combination, varying between individual patients, of obstructive bronchiolitis and parenchymal destruction (emphysema). The principal environmental risk factor for the development of COPD is exposure to tobacco smoke, but occupational or other exposure to some chemicals and both organic and inorganic dusts are also known to increase the risk.

The prevalence of COPD in the population is difficult to estimate, but it is a major public health problem. Mortality due to COPD is again difficult to estimate, but appears to be increasing. Between 1970 and 2002, deaths due to COPD doubled, in contrast to a decrease in deaths due to some other chronic diseases such as cardiovascular disease (Jemal et al 2005). This is probably due to two factors, namely the aging population, and the fact that COPD mortality lags trends in tobacco smoking by several decades. It is estimated that by 2020, COPD will be the third leading cause of global mortality (GOLD 2009).

The aims of pharmacological treatment in COPD, as described in the GOLD guideline are to prevent and control symptoms, to reduce the frequency and severity of exacerbations, to improve health status, and to improve exercise tolerance. GOLD guidelines recognize that bronchodilators (by reducing airflow limitation) are central to the management of symptoms in COPD and recommend regular use of long-acting bronchodilators for patients with moderate to severe COPD. Within the class of long-acting bronchodilators, long-acting β2 agonists (LABAs) and long-acting antimuscarinic are available. While there are several marketed LABAs such as formoterol, salmeterol and indacaterol, tiotropium is the only long-acting antimuscarinic (LAMA) currently available. LABAs and LAMAs are recommended first-line treatments in moderate to severe COPD. The addition of a glucocorticosteroid is recommended as additional therapy for severe COPD (GOLD 2010).

About the product

Glycopyrronium bromide, (abbreviated GP) is a competitive antagonist at muscarinic receptors in the autonomic nervous system. It has little or no activity against nicotinic receptors, the other main class of cholinergic receptors. Injectable and oral forms of GP exist and are marketed in several countries. GP has been used for a long time in anaesthesia as a preoperative antimuscarinic to reduce the volume and free acidity of gastric secretion, to block cardiac vagal inhibition reflexes and to protect against the peripheral muscarinic actions of anticholinesterases. GP is also used for treatment of hyperhidrosis (abnormally increased sweating). The oral GP formulation was approved in the United States in 2010 and is indicated for severe drooling in patients 3-16 years of age with neurologic conditions.

A dry powder formulation of glycopyrronium bromide has been developed as a once daily (o.d.) inhalation treatment for patients with chronic obstructive pulmonary disease (COPD) under the compound code NVA237. The clinical development program for NVA237 in patients with COPD provides the basis for evaluating the prolonged duration of action and clinical effects of the drug. A full toxicology and pharmacokinetics (PK) program has been conducted to support the clinical program.

NVA237 is to be administered once daily (o.d.) at a dose of 44 µg, as a capsule via a low resistance single dose dry powder inhaler (SDDPI), also referred to as 'Concept1'. One NVA237 capsule contains 50 µg of the active substance glycopyrronium (metered dose) and is delivered to the lung as an inhalation powder via the Breezhaler inhaler device. The delivered dose (the dose that leaves the mouthpiece of the Breezhaler inhaler) is equivalent to 44 µg glycopyrronium.

The applicant applied for the following indication: once daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

The approved indication was: maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The initial clinical development of glycopyrronium bromide was performed by Arakis using the Miat Monohaler, a device similar to the Concept1 device used by the Applicant in the current development program. A total of 292 patients with COPD received GP once-daily; data from these studies showed that inhaled glycopyrronium bromide is well-tolerated and suitable for use as a once-daily bronchodilator. These studies are not directly referred to, as Novartis conducted a stand-alone clinical development program using its own Concept1 device for all studies.

Type of Application and aspects of development

Glycopyrronium bromide is submitted as a full application referring to Article 8(3) in Directive 2001/83/EC via the optional scope of the centralised procedure for a known active substance in accordance with article 3(2)(b) (significant therapeutic innovation) in accordance to Regulation (EC) No 726/2004.

The applicant did not seek scientific advice at the CHMP.

2.2. Quality aspects

2.2.1. Introduction

Seebri Breezhaler is presented as an inhalation powder in hard capsules, containing glycopyrronium bromide as the active substance, glycopyrronium being the active moiety. Each capsule contains 63 µg of glycopyrronium bromide (metered dose), equivalent to 50 µg of glycopyrronium. The delivered dose (the dose that leaves the mouthpiece of the inhaler) is equivalent to 44 µg of glycopyrronium (55 µg of glycopyrronium bromide).

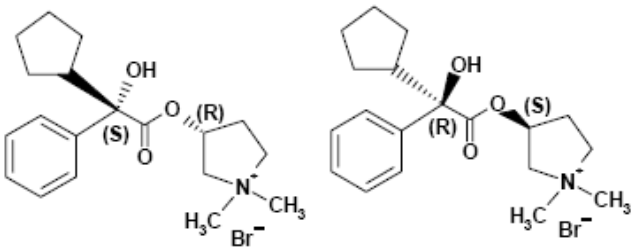
The product is presented in hypromellose hard capsules containing the active substance mixed with two excipients lactose monohydrate and magnesium stearate. The powder is enclosed in hard capsules composed of hypromellose, carrageenan, potassium chloride and Sunset Yellow FCF (E110). The capsules (size 3) are orange, transparent with black Novartis logo under black radial bar on cap and black 'GPL 50' above black radial bar on body. Printing ink consists of shellac and black iron oxide and several solvents which are removed during imprinting.

The capsules are packed in PA/alu/PVC – alu perforated unit dose blisters.

Seebri Breezhaler is a single-dose inhaler. Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

2.2.2. Active Substance

Glycopyrronium bromide, the active substance of Seebri Breezhaler, is a well known active substance, chemically designated as 3-(2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidinium bromide or (3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, and has the following structure:



It is a white, non-hygroscopic powder, freely soluble in water, soluble in ethanol (96%), very slightly soluble in methylene chloride. The substance is also freely soluble in simulated lung fluid (phosphate buffer pH 7.4).

Glycopyrronium bromide is a quaternary ammonium salt (ionic compound) and it is completely ionized between pH 1 and 14. It is a racemic mixture of the 3R,2S and 3S,2R stereoisomers. No optical rotation is seen in solution. Only single polymorphic form (crystalline Form A) has been reported.

The chemical structure of glycopyrronium bromide has been confirmed by means of UV, IR, ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry (MS). The content of carbon, oxygen, hydrogen, nitrogen and bromide has been determined by elemental analysis. The structure and stereochemistry of the active substance has been determined by means of X-ray crystallography.

Manufacture

The active substance is manufactured by a synthesis which consists of a number of chemical reaction steps followed by crystallisation and several re-crystallisation steps.

The manufacturing process has been described in sufficient detail including suitable reaction schemes. The amounts of raw materials, yields, and equipment have been specified, and the in-process controls have been well described. Appropriate specifications for starting materials and reagents have been proposed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification, including parameters, analytical procedures and acceptance criteria was considered suitable for release of batches of active substance. The specification complies with the requirements of the Ph. Eur. monograph and the Q3A (R), Q3C and Q6A ICH guidelines. Justifications have been presented for each of the requirements listed in the specification.

The specification includes tests for appearance, identification (IR, X-ray diffraction and HPLC), Impurities including stereoisomeric purity (HPLC), residual solvents (GC), loss on drying, sulphated ash, heavy metals, acidity or alkalinity, colour of solution, assay (HPLC or titration) and microbiological purity. The micronized active substance, stabilized by an added excipient, is controlled regarding particle size distribution and it is a critical quality parameter in relation to the finished product

The descriptions of the analytical methods are considered acceptable and their validations are performed in accordance with ICH standards and Ph. Eur. requirements.

Batch analytical data have been provided for batches of the active substance used in non-clinical, clinical and stability studies as well as batches manufactured at the production site using the proposed final manufacturing process. All batches comply with the proposed specifications. Batch analysis results confirm batch to batch consistency and support uniformity of the quality of the active substance.

Stability

Stability data from long term and accelerated stability studies on 6 batches covering storage periods up to 36 months, photostability testing and stress testing under different conditions were submitted.

Batches were also stored under intermediate condition to be tested if significant changes were seen under accelerated conditions. Studies were also made on the 6 batches stored in refrigerator and the batches were also stored in a freezer only to be tested if significant changes were seen after storage in the refrigerator.

The applicant has also submitted three months stability data at 25°C/60% RH and 40°C/75% RH for three production scale batches.

Stability program was supplemented by a photostability study, stress testing (storage for one month at 50°C, 60°C and 80°C), forced decomposition studies (3 day heated in aqueous solution under acidic, alkaline, neutral and oxidising conditions), isomerisation study (storage for one month at 50°C exposed to acid, alkaline and neutral conditions) and hygroscopicity (58% RH and 75% RH 1 week/80% RH and 93% RH 1 day).

Results obtained from the submitted stability program indicate very good stability of glycopyrronium bromide in the solid state. No evidence of instability was observed under long term or accelerated conditions when samples were stored in the proposed container closure system. Glycopyrronium bromide was not photosensitive.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The principle of the dry powder formulation for inhalation is the homogeneous attachment of fine particles of the active substance, present as a small percentage of the formulation, on the surface of comparatively coarse particles of a free-flowing inert carrier (lactose). During inhalation, the dry powder dose is entrained into the turbulent airflow generated in the Concept1 mouthpiece, leading to the detachment of the active substance particles from the surface of the coarse carrier particles. Once released from the carrier, particles of the active substance are inhaled and deposited into the lungs.

As the method of administration is by inhalation, particle size is critical and must be controlled to achieve the required lung deposition profile. Throughout the development the formulation used during phase II and III studies were identical in composition and this formulation is also the proposed commercial quantitative formula, apart from the capsule colours. Colourless clear capsules were used in the clinical studies vs. transparent orange capsules proposed for the commercial product. The performance of both capsules was compared and was shown to be equivalent based on aerodynamic particle size distribution and average delivered dose.

The finished product is administered with a single-dose dry powder inhaler 'Concept1', also referred to as the Breezhaler device. Concept1 is currently used for already marketed product Onbrez Breezhaler. The pharmaceutical performance of the inhalation powder, hard capsules in conjunction with the Concept1 inhalation device has been investigated. The Fine Particle Mass (FPM) and Delivered Dose Uniformity (DDU) were investigated at different flow rates (i.e. 30 to 100 L/min) covering well the relevant ranges for COPD patients' inspiratory flow rates through the low resistance Concept1 device.

A number of different studies have been performed to demonstrate the suitability of the device for this product including DDU and FPM over patient flow rate range, single dose fine particle mass, particle size distribution, actuator deposition, cleaning requirements, environmental moisture effects, robustness and device delivery development.

The device is intended for 30 days of use (30 doses). A Concept1 inhaler is provided in each pack and the SmPC (section 6.6) states that the inhaler should be disposed after 30 days of use.

The development of the product has been satisfactorily performed and explained and is in accordance with EU guidelines on Development pharmaceutics and EMEA/CHMP/QWP/49313/2005 Corr. on the Pharmaceutical Quality of Inhalation and Nasal Products. Particle size requirements for both active substance and excipients have been justified in terms of their contributions to finished product performance characteristics. Device cleaning has been properly addressed during the development and are reflected in the Product Information.

It is a Class I medical device and its conformity with directive 93/42/EEC concerning medical devices has been certified by Novartis Pharma AG in a 'declaration of conformity' dated October 2008.

The packaging materials have shown suitability by acceptable product performance characteristics and stability studies.

Adventitious agents

The supplier of lactose monohydrate certified that it is produced from milk obtained from healthy cattle under the same conditions as milk intended for human consumption.

Magnesium stearate is of vegetal origin and relevant certificates from manufacturers of this excipient have been provided.

Manufacture of the product

The manufacturing process of the finished product involves a preparation of a Pharmaceutical Intermediate (PI). In the next steps the PI is blended with excipients and the powder blend is filled into hard capsules.

The manufacture of the PI has been validated for 3 commercial scale batches using the same manufacturing facilities and equipment as intended for commercial batches. The quality of the PI is adequately controlled and based on the validation results a homogenous product, with the target product characteristics, is obtained with the manufacturing process described.

The manufacturing process has been validated for commercial scale batches, which is considered appropriate because of the pharmaceutical dose form and the manufacturing process. The final blend uniformity, content uniformity of the capsules through the encapsulation process, fine particle mass through the encapsulation process and delivered dose uniformity through the encapsulation process were evaluated. Operating parameters and in-process controls were studied to evaluate their effects on the final drug product properties. Based on this analysis, critical steps were identified and in-process control acceptance criteria were defined.

Data presented during the process evaluation indicate that the manufacturing process of the PI, inhalation powder hard capsules and the blistering process consistently yields bulk product, which meets the predetermined quality characteristics. Moreover, the chosen in process tests have been shown to be suitable for monitoring the manufacturing process.

The conclusion from the presented data was that the ranges and values chosen for the processing parameters were acceptable to support the commercial manufacture of the product. The manufacturing process is well controlled and capable of producing a product of consistent quality.

Product specification

The product specification includes tests for appearance of capsules and the contents (visual), fine particle mass (Next Generation Impactor), identification (TLC and HPLC), uniformity of delivered dose (HPLC), degradation products (HPLC and HPLC-MS), loss on drying (halogen dryer), uniformity of dosage units: content uniformity by content uniformity (HPLC), assay (HPLC) and microbial purity.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods. The analytical methods have been validated in accordance with ICH guidelines.

Batch analysis data have been provided on 11 production scale batches from the proposed commercial manufacturing site, demonstrating compliance with the proposed release specification. The results comply with the specification and confirm consistency of the product.

Stability of the product

Stability studies have been conducted on three batches manufactured at the intended site of manufacture, at the intended production scale and packaged in the proposed container closure system. The stability studies have been carried out according to ICH requirements. Batches of the finished product were stored under the long term conditions (25°C/60% RH), intermediate conditions (30°C/65% RH) and accelerated conditions (40°C/75% RH). In addition one batch was been stored in refrigerator (5°C/ambient) and freezer (-20°C/ambient).

Stability program included also testing of the intermediate product and bulk capsules.

No significant changes were observed during the stability studies. On the basis of the provided stability data, the assigned shelf life and storage conditions as defined in the SmPC is well supported.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Seebri Breezhaler inhalation powder, hard capsule is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted in support of the marketing authorisation application.

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data.

Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the finished product has been presented.

The formulation is considered justified. The excipients are well established and used in acceptable quantities. Their function has been satisfactorily documented.

The method of manufacture has been satisfactorily described, including holding times and in-process tests. The data shows consistent manufacture and is considered sufficient for this manufacturing process.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory manner.

There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

A full nonclinical programme has been conducted to support the clinical program. The safety pharmacology studies as well as pivotal toxicology studies were all conducted in compliance with GLP regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacology studies

Based on studies in transfected Chinese hamster ovary (CHO) cells, the binding affinity constants and rate parameters of NVA237 and its enantiomers were determined at the human M1, M2, M3, M4 and M5 muscarinic acetylcholine receptors (mACh). The affinity of NVA237 towards the muscarinic receptors was M1 (Ki = 0.15 nM)> M3 > M2/M4 > M5. Moreover, the majority of the biological activity resides in the [3S, 2R] enantiomer of NVA237 which has 100-fold greater activity for the M3 receptor than the [3R, 2S] enantiomer.

The anti-cholinergic bronchodilator tiotropium displayed higher binding affinity towards the M1, M2, M3, M4 and M5 receptors than NVA237 at 37°C in an assay buffer containing physiological sodium ion concentration. Hence, NVA237 displayed a 10-fold lower affinity towards the M3 receptor than tiotropium. Although the M1 to M4 receptors have been identified in the human lung, the excitatory M3 receptors located on airway smooth muscle cell are considered the prime mediators of cholinergic bronchoconstriction.

The faster dissociation rate of NVA237 (k_{off} = 0.07 ± 0.004) compared to tiotropium (k_{off} = 0.015 ± 0.002) at the M3 receptor indicates that NVA237 will have a shorter dissociation half life than tiotropium ($t_{½}$ = 9.9 versus 46.2 minutes). Considering the relatively short half lives, it is likely that other factors contribute to the extended duration of action of NVA237 and tiotropium than M3 receptor residency time.

The receptor kinetic data suggest that at equi-effective concentrations, NVA237 will reach equilibrium faster than tiotropium bromide and thus potentially demonstrate a faster onset of action. This assumption was based on calculations of the time taken for NVA237 and tiotropium to associate to 50% of the receptor population ($t_{1/2}$ for association = $0.693/(k_{on}.[ligand]+k_{off})$), which is 6.2 minutes for NVA237 versus 23.9 minutes for tiotropium at their respective K_d concentrations.

In vivo pharmacology

The efficacy and duration of action of different formulations (aqueous, dry powder and controlled release) of NVA237 on methacholine-induced bronchoconstriction were evaluated in anaesthetized rabbits. Administration of methacholine (10 µg kg^{-1}, IV) evoked an increase in pulmonary inflation pressure and was associated with a decrease in heart rate which was accompanied by a fall in mean arterial blood pressure. Intra-tracheal (IT) administration of all the formulations of NVA237 or ipratropium tested inhibited the increase in pulmonary inflation pressure evoked by methacholine administration by approximately 90%. However, only ipratropium attenuated the cardiovascular response mediated by methacholine. Aqueous and dry powder formulations of NVA237 (20 µg IT) as well as ipatropium (20 µg IT) exhibited a duration of action of 6 hours. The controlled released formulation increased the duration of action when compared to a comparable dose (10 µg IT) of the dry powder formulation by 50%.

The aim of a second study in anaesthetized rabbits was the efficacy and duration of action of tiotropium on methacholine-induced bronchoconstriction as well as potential side-effect on the cardiovascular system. Intra-tracheal administration of tiotropium (3 µg) attenuated the increase in pulmonary inflation pressure as well the bradycardia and the hypotension evoked by methacholine administration. In contrast to tiotropium and to some extent also ipratropium, IT administration of NVA237 did not significantly affect neither heart rate nor mean blood pressure.

Moreover, the ability of the NVA237 to suppress methacholine-induced bronchoconstriction was investigated in spontaneously breathing, anaesthetised rhesus monkeys and the effects compared with those seen following tiotropium and ipratropium. NVA237 was administered as an aerosol at mean dose levels of 0.05, 0.15, 0.31 and 0.61 µg/kg intratracheally (IT). NVA237 induced dose-, and time-dependent inhibition of methacholine-induced bronchoconstriction with the maximal response observed 15 minutes following drug inhalation (first time point). Around 80% inhibition of bronchoconstriction was observed 15 minutes following the start of inhalation of 0.31 µg/kg NVA237 and 0.014 µg/kg tiotropium, respectively. Similarly, 15 minutes following start of inhalation, approximately 90% inhibition of bronchoconstriction was observed for 0.96 µg/kg ipratropium. Tiotropium (0.14 µg/kg IT) exerted the most potent inhibition of methacholine-induced bronchoconstriction with around 80% inhibition of bronchoconstriction still observed around 5 hours post-dosing. NVA237 and ipratropium (0.61 and 0.96 µg/kg IT, respectively) displayed a lower potency with only 65% and 35% inhibition of bronchoconstriction at approximately 5 hours post-dosing.

NVA237 and tiotropium were compared in anaesthetized Brown Norway rats IV administered methacholine (0.03, 0.1, 0.3, 1, 3, 10, 30, 100 µg kg^{-1} at 5 minute intervals) with respect to effects on lung function, salivation and cardiovascular parameters. The effects were evaluated at 1, 6 and 24 hours following drug treatment. Tiotropium was the most potent inhibitor of methacholine-induced bronchoconstriction hence at 24 hours post-dosing the ED_{50} values for NVA237 and tiotropium were 1.2 and 0.14 µg/kg, respectively. However, at all the time points studied, NVA237 demonstrated an improved therapeutic index with respect to effects on salivation, hypotension and bradycardia. Hence, 1 hour post-dosing, the therapeutic index varied from 8.8 to 28-fold for NVA237 and from 1.5 to 4.2 for tiotropium.

Glycopyrronium is a racemate (i.e. a 1:1 mixture) of the two enantiomers QBA608 ([3S, 2R]-threo-isomer) and QBA609 ([3R,2S]-threo-isomer. Although the M1 to M3 receptors have been identified in the human lung, the excitatory M3 receptors located on airway smooth muscle are considered the prime mediators of cholinergic bronchoconstriction. Based on pharmacological considerations, an ideal anticholinergic bronchodilating agent would inhibit only the M1 and M3 receptors and spare the M2 receptors as the latter is believed to protect against parasympathetic-mediated bronchoconstriction. The binding affinity constants (pKi values) for glycopyrronium binding to the muscarinic acetylcholine receptors M1, M2, M3, M4 and M5 were 9.69, 9.25, 9.64, 9.06 and 8.91, respectively. Hence, glycopyrronium displays around 2.5-fold higher binding affinity towards the M1 and M3 receptors when compared to the M2 receptor. Functional studies demonstrated that glycopyrronium exerts an antagonistic effect at the muscarinic acetylcholine receptors while no agonistic effect was observed at concentrations up to 10 µM.

The majority of the biological activity resides in the [3S, 2R] enantiomer of NVA237 which has 100-fold greater activity for the M3 receptor than the [3R, 2S] enantiomer.

The anticholinergic bronchodilator tiotropium displayed higher binding affinity towards the M1, M2, M3, M4 and M5 receptors than glycopyrronium. Hence, glycopyrronium displayed a 10-fold lower affinity towards the M3 receptor than tiotropium.

The faster dissociation rate of glycopyrronium (koff = 0.07) compared to tiotropium (koff = 0.015) at the M3 receptor indicates that glycopyrronium will have a shorter dissociation half life than tiotropium

(t½ = 9.9 and 46.2 minutes, respectively). Considering the relatively short half lives, it is likely that other factors contribute to the extended duration of action of glycopyrronium and tiotropium than M3 receptor residency time.

Receptor kinetic data suggest that at equieffective concentrations, glycopyrronium will reach equilibrium faster than tiotropium bromide and thus potentially demonstrate a faster onset of action. This assumption was based on calculations of the time taken for glycopyrronium and tiotropium to associate to 50% of the receptor population, which is 6.2 minutes for glycopyrronium versus 23.9 minutes for tiotropium at their respective Kd concentrations.

The efficacy and duration of action of intratracheally (IT) administered glycopyrronium and the anti-cholinergic bronchodilators ipatropium and tiotropium on methacholine-induced bronchoconstriction were evaluated in anaesthetized rats, rabbits and rhesus monkeys. Intravenous administration of methacholine evokes an increase in pulmonary inflation pressure and is associated with a decrease in heart rate, which is accompanied by a fall in mean arterial blood pressure. Intratracheal administration of glycopyrronium, ipratropium and tiotropium inhibited the increase in pulmonary inflation pressure evoked by methacholine administration by approximately 80 to 90%. In anaesthetized rhesus monkeys, tiotropium (0.14 µg/kg IT) exerted the most potent inhibition of methacholine-induced bronchoconstriction with around 80% inhibition of bronchoconstriction still observed around 5 hours post-dosing. Glycopyrronium and ipratropium (0.61 and 0.96 µg/kg IT, respectively) displayed a lower potency with only 65% and 35% inhibition of bronchoconstriction at approximately 5 hours post-dosing. Tiotropium was the most potent inhibitor of methacholine-induced bronchoconstriction in anaesthetized rats, hence at 24 hours post-dosing the ED50 values for glycopyrronium and tiotropium were 1.2 and 0.14 µg/kg, respectively.

However, at all the time points studied, glycopyrronium demonstrated an improved therapeutic index with respect to effects on salivation, hypotension and bradycardia. Hence, 1 hour post-dosing, the therapeutic index varied from 8.8 to 28-fold for glycopyrronium and from 1.5 to 4.2 for tiotropium.

Secondary pharmacodynamic studies

In guinea pig and human isolated tracheal smooth muscle studies, NVA237 (10 nM) was shown to have no effect on neurokinin A-induced contraction (1 µM, n=4), indicating the selectivity of NVA237 for cholinergic pathways (Villetti et al., 2006).

The individual enantiomers of NVA237 were evaluated for activity in a wide range of enzyme and radioligand binding assays. No activity was observed in the panel of enzyme assays for both enantiomers. At 10 µM both enantiomers partially inhibited ligand binding at the Sigma σ1 receptor; however the reduced potency in comparison to binding at the M3 muscarinic receptor (approximately 10,000 fold) indicates that this off target binding will not occur at pharmacological doses. The metabolite M9 (CJL603) is a racemic carboxylic acid derivative formed by hydrolysis of NVA237. A single enantiomer of metabolite M9, QAW665, was assessed for its muscarinic (M1-M5) and off-target activity in a panel of 65 G-protein coupled receptors, transporters, ion channels and enzymes. No significant binding to any of these targets was found up to a concentration of 10 µM, indicating that QAW665 lacks pharmacological activity.

In enzyme and radioligand bindings assays, the glycopyrronium [3S,2R] and [3R,2S] enantiomers did not display activity towards a range of potential secondary targets. Moreover, the glycopyrronium metabolite M9 was devoid of activity against muscarinic receptors (M1-M5) and a wide panel of G-protein coupled receptors, transporters, ion channels and enzymes.

Safety pharmacology programme

In safety pharmacology studies no treatment related effects were seen on the central nervous system (except for slight and transient pupil dilation) or respiratory system in rats at an inhaled dose of 0.168 mg/kg glycopyrronium (i.e., >30-fold the recommended clinical dose based on the human equivalent dose).

Inhibition of the hERG current was only observed at concentrations significantly higher than the maximum human exposure (Cmax) at the recommended clinical dose. Following administration of 0.01 mg/kg IV (i.e., a 4-fold higher plasma exposure level than that observed clinically based on AUC data), transient effects were seen on heart rate and blood pressure in Beagle dogs. Following an inhaled dose of 0.149 mg/kg (i.e., >100-fold the recommended clinical dose based on allometric scaling using body surface area), transient increases in heart rate and transient decreases in heart rate-corrected QT-intervals were observed. However, also PR and P widths were affected at this dose. Moreover, tachycardia was a frequent finding in the dog repeat-dose toxicity studies.

Pharmacodynamic drug interactions

No studies of pharmacodynamic drug interaction have been performed which was considered acceptable from a non-clinical perspective given the lack of binding to other drug targets, the vast clinical experience with inhaled anti-muscarinic drugs in respiratory medicine and the lack of NVA237 induced inhibition or induction of CYP450 enzymes or other transporters.

2.3.3. Pharmacokinetics

Bioanalytical methods

LC-MS/MS methods were used to evaluate the concentration of glycopyrronium in plasma of mice, rats, rabbits and dogs. Although some deficiencies were identified in the validation procedures (e.g., inter-assay variability was generally not investigated, and limited number of replicates, e.g., less than 5 replicates at each concentration), the performance of the methods (i.e., sensitivity and reproducibility) are considered acceptable for regulatory purposes.

Stability was demonstrated in mouse, rat and dog plasma for up to at least 10 weeks during sample storage at -20°C.

Improper handling of samples and/or ineffective cleaning of the auto sampler system led to carry-over in the validation studies, which could account for at least a 10% contamination of the blank samples. In several of the pivotal toxicity, the drug substance was detected in plasma samples obtained from the control group. These observations could probably be explained by improper handling/cleaning. The effect on the conclusions of the individual studies is discussed in the Toxicology section.

The pivotal toxicity studies were performed using validated bioanalytical assays.

Absorption

Pharmacokinetic investigations were only conducted in male rats. The interspecies and exposure analysis relies primarily on the TK data. Due to the lack of pharmacokinetic parameters such as $T_{½}$, conclusions concerning exposure should preferably be based on AUC data in the pivotal toxicity studies.

The absolute bioavailability of inhaled glycopyrronium was approximately 40% in humans, which is considerably lower than that observed in rats following IT application (96%). The absolute oral bioavailability of glycopyrronium was low in both rats and humans (≤5%). This means that the

majority of the swallowed dose fraction following inhalation of glycopyrronium in humans is either subject to extensive first-pass metabolism or not absorbed and excreted in the faeces.

Following administration of the racemic compound, the exposure to the two enantiomers QBA608 and QBA609 was nearly similar in rats and dogs. Nevertheless, there was general tendency to a slightly higher exposure to the QBA608, which may be due to the presence of an enantiomer-specific process for QBA608 but not for QBA609. However, this hypothesis has not been pursued further by the applicant. Furthermore, there was also some limited evidence of inter-individual variability in terms of chiral interconversion.

The disposition of the enantiomers in humans following inhalation of glycopyrronium was characterized by measuring the excretion of the enantiomers in urine (the lower LOQ was 250 pg/mL for each enantiomer in urine as compared with 3-4 pg/mL for the racemic compound in plasma). The amounts excreted and the excretion rates of the two enantiomers were similar. In both COPD patients and healthy volunteers and after single and repeated dosing of NVA237, the mean QBA608/QBA609 ratios was close to 1.0 (range 0.85-1.04).

The formation of the diastereomers QBI596 and QBI597 could not be demonstrated, neither in rat plasma nor in human urine.

The maximum concentration C_{max} of glycopyrronium was generally observed at completion of the inhalation period; except in rabbits, where the individual T_{max} ranged from 2 to 24 hours after the start of the inhalation exposure indicating a possible time-delayed absorption in this species.

The exposure to glycopyrronium increased with increasing doses in a roughly proportional manner although a trend of under-proportionality was noted in several studies. Generally, no systemic accumulation was noted in the toxicology species rat and dog following repeated dosing (in contrast to pregnant rabbit). Local accumulation in the lung was noted following repeated dosing in rats (not investigated in other species).

No obvious gender differences were observed during the toxicokinetic investigations. Hence, the use of males only for the majority of the pharmacokinetic studies is considered acceptable.

The disposition of glycopyrronium was characterised by a multi-exponential decline in rats and humans. After inhalation, the apparent terminal half-life differed between the clinical studies with means between 13 and 57 hours, whereas no reliable terminal half-lives have been estimated in the animal species.

Distribution

Following IV administration of radiolabelled glycopyrronium, total radiolabelled components were located extravascularly and rapidly distributed throughout the body. High levels of radioactivity were observed in highly perfused tissues (kidney, liver, small intestine and various glands) Although glycopyrronium-related material was eliminated fast from most tissues, several tissues (eye, brown fat, Harderian gland, kidney and liver) had a significantly slow elimination.

In pigmented mice and rats, radioactivity levels in the eye and skin were generally above those observed in blood. This indicates that the radiolabelled components were taken up and retained in melanin-containing structures. The uptake was at least partly reversible. Otherwise, distribution in non-pigmented and pigmented rats was generally comparable. Furthermore, the distribution was comparable following IT, IV and PO administration; only measurements in gastro-intestinal-related tissues were qualitatively higher following PO administration.

Glycopyrronium binds weakly to plasma proteins (range 23-44%) in all species tested (i.e., mice, rats, rabbits, dogs, and humans). Generally, the plasma protein binding was comparable between the

species although the values were slightly higher for rabbits and humans. Hence, the free drug concentrations are expected to be slightly higher in the toxicological species than in humans. Binding studies conducted with purified human serum albumin and α1 acid glycoprotein indicated that the observed plasma protein binding in humans cannot solely be explained by binding to these two proteins. Although a slight concentration-dependency in plasma protein binding was observed in all species, it is considered without any relevance for the interpretation of the safety data.

The blood/plasma concentration ratios were comparable between species (0.48-0.67) with no apparent concentration-dependency. Plasma is a suitable matrix for monitoring of glycopyrronium as it mainly distributed into the plasma fraction of blood.

No or limited placenta transfer was observed in pregnant mice, rabbits, dogs and humans. Glycopyrronium and its metabolites distributed well into milk from lactating rats and generally reached higher concentrations in milk when compared with those observed in plasma (up to 11.3 times). Its significance to humans is unknown.

Metabolism

The *in vivo* metabolic profile (plasma, urine and faeces) of glycopyrronium was thoroughly investigated in mice and rats following IV, PO and IT (only rats) administration. Furthermore, the metabolites in milk (M) and bile (B) were investigated in lactating and bile duct-cannulated rats. Glycopyrronium is extensively metabolised in rodents. There were some quantitative differences in the metabolic profile in rodents depending on the route of administration. The differences were most pronounced for the parent drug and the metabolites found in significant amounts in plasma (i.e., >2% of the total AUC; M8, M9, M10, M16, M17, M20, M38, M40, M41 and M42). Regardless, glycopyrronium and its metabolite M9 constituted the majority of the plasma exposure in mice and rats. Following PO administration, metabolism was the major route of elimination. This is not surprising considering the low bioavailability following PO administration.

Human systemic exposure to M9 (CJL603) was on average in the same order of magnitude as the exposure to parent drug after inhalation. In humans, M9 was only of minor importance after IV administration. Moreover, only minimal amounts of M9 were found in the urine after both routes of administration.

The *in vitro* metabolism of glycopyrronium was investigated in mouse, rat (two strains), rabbit, dog and human hepatocytes in addition to liver and lung microsomes obtained from rat, dog and human. Quantitative, but no qualitative differences were observed between species. However, no unique human metabolites were identified *in vitro*. Clinically, there are no indications for the existence of unidentified human metabolites. Overall, it is considered unlikely that metabolites of glycopyrronium contribute significantly to the efficacy or safety of product.

Only low metabolism was seen when glycopyrronium was incubated with recombinant human CYP2D6 enzymes. Furthermore, the *in vitro* studies did not show lung metabolism in the species tested (rat, dog and human).

No chiral interconversion of QBA608 and QBA609 was detected *in vitro* using rat, dog and human hepatocytes. However, the data is difficult to assess as the raw data or representative mass spectra are not available. Furthermore, it is not obvious whether the method of analysis used for studying the interconversion was validated. The Lower LoQ has been stated as 1 ng/mL (rat matrix) in the report. No chiral interconversion of QBA608 and QBA609 was detected *in vitro* in rat microsomes using a semi-validated method analysis with a lower LoQ of 5 ng/mL.

Chiral interconversion was observed *in vivo* in rats (see Absorption section).

Excretion

The excretion of glycopyrronium was investigated in mice and rats (including bile duct-cannulated) following IT (rat only), IV and PO administration.

Following IV administration, the glycopyrronium was mainly eliminated via urinary excretion (46-68%) and to a lesser extent via bile/faeces (<40%). The radioactivity could mainly be ascribed to unchanged drug in both faeces and urine accounting for about 50-60% and 25-65% of the total detected radioactivity, respectively. These data indicate that both the metabolic and biliary elimination are less important elimination pathways as compared to the urinary excretion.

Following IT and PO administration, glycopyrronium was mainly excreted via faeces (>50% and >90%, respectively). It is likely that the majority of the swallowed dose is not absorbed (and hence directly excreted in the faeces) considering 1) the low biliary excretion in bile duct-cannulated rats following IV administration (~7%), 2) the low oral bioavailability observed in rats and humans following PO administration, and 3) the fact that the majority of the radioactivity in faeces from rodents could be ascribed to unchanged drug (>60% of the detected radioactivity) following PO administration.

The excretion of glycopyrronium was investigated in humans following IV and IH administration. In humans, urinary excretion was the major route of elimination (accounting for 61-85% of the dose). Non-renal clearance was mainly due to metabolism as limited biliary clearance (approximately 5% after IV administration) was observed. Furthermore, no major species-differences in excretion were identified based on the available data.

Following inhalation in humans, part of the administrated dose will be distributed to the lung and part will be swallowed orally. However, the gastrointestinal absorption of glycopyrronium is unlikely to contribute significantly to the total systemic exposure.

Pharmacokinetic drug interactions

In vitro cytochrome P450 enzyme inhibition

The potential of NVA237 to inhibit human CYP enzyme activity was assessed using pooled human liver microsomes using several probe substrates whose metabolism is known to be CYP enzyme-selective. NVA237 showed very weak inhibition of CYP2D6 (IC50=100 µM) and CYP3A4/5-dependent midazolam hydroxylation (IC50≈230 µM estimated by extrapolation of experimental data). Very little or no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1 and CYP3A4/5-dependent testosterone hydroxylation activities was observed at NVA237 concentrations of up to 200 µM.

In vitro transporter inhibition

The potential of NVA237 to inhibit human ATP-binding cassette (ABC) transporter-mediated efflux via the multidrug-resistant protein 1 (MDR1), the breast cancer resistant protein (MXR, BCRP) and the multidrug resistance-associated protein 2 (MRP2) was investigated in recombinant MDCKII cells using the probe substrates cyclosporine A (for MDR1), mitoxantrone (for MXR) and valsartan (for MRP2). NVA237 was found to be no inhibitor of MDR1, MXR and MRP2 in all concentrations investigated (i.e., up to 300 µM).

The potential of NVA237 to inhibit human transporter-mediated uptake via the organic cation transporter 1 (OCT1), and the organic cation transporter 2 (OCT2) was investigated in HEK293 cells transiently transfected with OCT1 or OCT2. NVA237 was identified as a substrate for OCT1 and OCT2 with a Km of 125 µM and 119 µM respectively, and as an inhibitor of OCT1 and OCT2 with IC50 values of 47 and 17 µM, respectively.

The accumulation of [14C]-NVA237 (11.8 µM) into HEK Flp-In cells stably expressing human multidrug and toxin extrusion transporters hMATE1 and hMATE2K was investigated in vitro in parental HEK Flp-In cells. The MATE substrate/inhibitor tetraethylammonium (200 µM) completely inhibited hMATE1-

mediated [14C]-NVA237 transport. Conversely, the uptake of [14C]-NVA237 into HEK Flp-In cells stably expressing hMATE2K was not higher than the uptake into parental cells. These data suggest that NVA237 is a substrate of hMATE1, which may partly explain the renal clearance of NVA237 in humans in vivo. There is a potential for inhibitors of hMATE1 to affect the renal excretion of NVA237 and its pharmacokinetics.

In vitro induction of 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. Induction of mRNA, relative to the vehicle control, was determined by real-time PCR (RT-PCR) and evaluation of changes in CYP enzyme activities were assessed after the induction period by quantitative LC/MS/MS analysis of CYP-selective probe substrate metabolism. NVA237 at concentrations of up to 50 nM was determined not to be an inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 enzyme activity in hepatocytes. In addition, NVA237 did not induce CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, UGT1A1, MDR1, or MRP2 mRNA.

In vitro uptake of NVA237 into human hepatocytes

The potential active uptake of NVA237 by hepatocytes was studied in 3- to 4-day primary cultures of human hepatocytes. Hepatic uptake was in a low range with human hepatic clearance around 7 µL/min/mg. The data indicated human hepatocyte uptake of NVA237 occurs, most likely, solely by a slow passive permeation process.

In vitro intestinal transport in the gastrointestinal Caco-2 cell line

The permeability of NVA237 across the intestinal barrier was investigated using the Caco-2 model system. Based on total radioactivity, no substantial differences between apical-to-basolateral (AP-BL) and basolateral-to-apical (BL-AP) permeabilities of NVA237 were observed for all tested concentrations (5 - 200 µM). Standard inhibitors of efflux pumps had no significant effect on the AP-BL permeabilities of NVA237. Further HPLC analysis of specific NVA237 samples revealed that only ~ 1 % of the radioactivity in the receiver compartment accounted for CJL603, while the major part of radioactivity was identified as the parent NVA237. It was concluded that NVA237 permeates passively at a low rate through Caco-2 monolayers without involvement of drug transporters. The predictive absorption was less than 30%.

Concerning the maximum plasma concentration of 0.5 nM for glycopyrronium following administration of the maximum recommended human dose, it is considered unlikely that glycopyrronium should behave as a victim or perpetrator drug for a broad panel of cytochrome P450 enzymes and various transporters (MDR1, MXR, BCRP, MRP2, OCT1, OCT2 and hMATE2K). The only exception is the renal and hepatic transporter hMATE1 for which it cannot be excluded that inhibitors may affect the pharmacokinetics of glycopyrronium. However, the clinical relevance cannot be assessed as the affinity of glycopyrronium for hMATE1 is presently not known.

The *in vitro* data also indicated that the disposition of glycopyrronium is mainly mediated via passive diffusion.

Mg-stearate uptake in rat lung precise-cut slices

Mg-stearate is an excipient used in the dry-powder formulation of Seebri Breezhaler (daily exposure 37 µg/day). [3H4]-Mg-stearate was dissolved in culture medium containing 10% fetal calf serum and incubated with rat lung slices up to 24 hours at 4°C and 37°C. A significant difference in tissue uptake (4% versus 43%) was observed between 4°C and 37°C, respectively, suggesting the contribution of an active process involving transporters or others cell mechanisms. No differences in cell viability were

observed using an ATP bioluminescence assay, indicating that [3H4]Mg-stearate is not toxic for lung cells at the tested concentration (4.81 µM [salt] or 10 µM [free acid]) over 24 hours.

Mg-stearate is likely to be dissolved into the lung surfactant and taken up into the lung tissue. Following cell uptake, stearic acid is assumed to undergo lipid metabolism.

2.3.4. Toxicology

Single dose toxicity

Extensive data are reported in the literature for glycopyrronium bromide following single PO, intra-peritoneal (IP) or IV administrations to mice, rats, rabbits, cats and dogs. Single dose investigations were also included in dose-range finding studies during an IV cardiovascular safety pharmacology study in dogs (Study 0510129) and a 1-week inhalation toxicity study in dogs (Study 852240). These studies revealed clinical signs that included mydriasis, tachycardia, prostration, anorexia and diarrhoea consistent with exaggerated pharmacological effects and, at very high doses, drug-induced deaths.

Repeat dose toxicity

The results from repeat-dose inhalation toxicity studies conducted in rats and dog are tabulated in the table below. The achieved doses are expressed in terms of the ammonium cation of glycopyrronium bromide. Moreover, the mass median aerodynamic diameters values given in the table are based on chemical analysis.

The following parameters were evaluated in the pivotal repeat-dose toxicity study in rats (26-weeks): clinical signs, body weights, food consumption, ophthalmology, haematology, clinical biochemistry, urinalysis, toxicokinetics, gross observations at necropsy, organ weights and histopathology. In the pivotal repeat-dose toxicity study in dogs (39-weeks) the following parameters were evaluated: clinical signs, body weights, food consumption, ophthalmology, electrocardiography, respiratory minute volumes, haematology, clinical biochemistry, urinalysis, toxicokinetics, organ weights and gross observations at necropsy, histopathology, mask aerosol concentrations and particle size analysis.

Overview of the repeat-dose toxicity studies conducted with NVA237. The doses are given as glycopyrronium base.

Study ID **GLP status** **Duration**	**Species** **N**	**Achieved dose/ (mg/kg/day)** **Route** **Formulation** **MMAD range**	**NOAEL (mg/kg/ day)**	**Major findings**
RATS				
0848191 GLP 1 week	Wistar rats 5/sex/group	0, 1.57, 3.41, 7.30/13.16 Nose only inhalation 2%, NVA237, 0.25% magnesium stearate, 97.75% lactose 2.14-2.31 µm	<1.96	**≥ 1.57 mg/kg/day** Mydriasis, ↓ food consumption, squamous metaplasia and minimal keratosis of the larynx, cases of squamous hyperplasia and chronic inflammation in the submucosa of the larynx **7.30/13.16 mg/kg/day** ↓ body weight, ↑ water:food ratios in ♀
0848192	Wistar rats	Air control,	0.49	**≥ 0.08 mg/kg/day**

Study ID **GLP status** **Duration**	**Species** **N**	**Achieved dose/ (mg/kg/day)** **Route** **Formulation MMAD range**	**NOAEL (mg/kg/ day)**	**Major findings**
GLP 4-weeks + 2-weeks recovery	Main: 12/sex/group Recovery: 8/sex/group	vehicle, 0.08, 0.49, 3.39 Nose only inhalation 5% NVA237, 0.25% magnesium stearate, 94.75% lactose monohydrate 1.42-3.09 µm		Mydriasis, ↓ body weight gain ♂, ↓ food:water ratio ♀, ↓ salivary gland weight ♂, mandibular glands (acinar atrophy), larynx (minimal squamous metaplasia), Hardarian glands (dose-dependent increase in porphyrin deposition accompanied by acinar hypertrophy) **≥ 0.49 mg/kg/day** Parotid gland (acinar diffuse hypertrophy at minimal to moderate severity), nasal cavities (hyaline inclusions in the propria mucosa of the olfactory respiratory epithelium) **3.39 mg/kg/day** ↓ Food consumption, ↓ food:water ratio, ↓ body weight gain, weight loss **Recovery** increased body weight gain, hyaline inclusions in the propria mucosa of the olfactory/respiratory epithelium persisted, partial recovery of squamous metaplasia in the larynx, partial recovery of acinar hypertrophy in the parotid gland
0580297 GLP 26-weeks + 4-weeks recovery	Wistar rats Main: 20/sex/group Recovery: 10/sex/group	Air control, vehicle, 0.07, 0.54, 3.98 Nose only inhalation 8% NVA237, 1% magnesium stearate, 91% lactose monohydrate 2.1-3.0 µm	0.07	**≥ 0.07 mg/kg/day** Larynx (squamous metaplasia of the epithelium at the base of the epiglottis), nasal cavities (eosinophilic globules in the respiratory/olfactory epithelium and hypertrophy/hyperplasia of goblet cells), porphyrin deposition **≥ 0.54 mg/kg/day** ↓ Body weight gain, mydriasis, lenticular changes (opacities, prominent suture lines, cataracts), lungs (epithelial hypertrophy at the bronchiolalveolar junction), nasal cavaties ♂ (exudate, inflammation, squamous metaplasia of the respiratory epithelium and degeneration of the olfactory epithelium) **3.98 mg/kg/day** ↓ Food consumption, Recovery: ↑ Body weight gain, ↑ food consumption, partial recovery of lenticular changes, partial recovery of squamous metaplasia of the larynx, no recovery in incidence or severity of eosinophilic globules in goblet cell in the nasal cavity, partial recovery of goblet cell hypertrophy/hyperplasia in the nasal cavity, minimal degeneration of the olfactory epithelium observed in a few animals.
DOGS				
0852240 Non-GLP 1-week DRF study	Beagle dogs 1/sex/group	0.06, 0.26 and 1.04 Face-mask	0.06	**≥ 0.06 mg/kg/day** Dryness of the nose and oral mucus membranes

Study ID GLP status Duration	Species N	Achieved dose/ (mg/kg/day) Route Formulation MMAD range	NOAEL (mg/kg/ day)	Major findings
		snout-only inhalation 5% NVA237, 0.25% magnesium stearate, 94.75% lactose monohydrate MMAD: 1.73-2.87 µm		**≥ 0.26 mg/kg/day** ↓Food consumption until the diet was moistened with water, swelling of the salivary glands, mydriasis, tachycardia, acinar hypertrophy in the mandibular and pharyngeal salivary glands **1.04 mg/kg/day** ↓ Food consumption even when the diet was moistened with water, ↓body weight, redness of sclera ♀, necrotizing inflammation of the larynx ♂
0852241 GLP 4-week + 2-weeks recovery	Beagle dogs Main: 3/sex/group Recovery: 2/sex/group	Air control, vehicle control, 0.024, 0.077, 0.25 Face-mask snout-only inhalation 5% NVA237, 0.25% magnesium stearate, 94.75% lactose monohydrate MMAD: 1.61-1.82 µm	0.024	**≥ 0.024 mg/kg/day** Corneal epithelial desquamation (minimal at all dose levels) **≥ 0.077 mg/kg/day** Low food consumption, pupils unresponsive to light, tachycardia, sublingual gland ♂ (basophilic acini) **0.25 mg/kg/day** ↓ Body weight ♀, ↑ salivary gland weight, ↓ testis & prostate weight, corneal opacity in 3/6 animals (also observed in 1/6 vehicle animals), sublingual gland (acinar hypertrophy, basophilic acini), pharynx ♀ (hypertrophy of mucinous acini in submucosal glands), lacrimal glands ♂ (acinar hypertrophy), eyes ♀ (minimal focal corneal ulceration), snout (↑ incidence of epithelial hyperkeratosis, epithelial erosions), ↑ incidence of hepatocellular hypertrophy **Recovery**: Still a slight increase in salivary gland weight, acinar hypertrophy in sublingual gland still observed in 1 ♂ dog, minimal focal corneal ulceration in 1 ♀
0670548 GLP 39-week + 4-week recovery	Beagle dogs Main: 4/sex/group Recovery: 2/sex/group	Air control, vehicle control, 0.02, 0.09, 0.27 Face-mask snout-only inhalation 8% NVA237, 1% magnesium stearate, 91% lactose monohydrate MMAD: 2.1-2.3 um	0.02	**≥ 0.02 mg/kg/day** ↓Lacrimal gland secretion (Schirmer tear test) **≥ 0.09 mg/kg/day** Red eyeballs, ↓body weight gain ♂ associated with ↓ body weight at week 39, tachycardia, ↑adrenal weight ♂, lacrimal gland ♂ (hypertrophy of secretory cells), pharynx (ectasia of the ducts and/or alveoli of the submucosal glands in ♂ accompanied by minimal inflammation in the ducts of the submucosal pharyngeal glands), salivary gland ♂ (hypertrophy of secretory cells), eyes (opacity) **0.27 mg/kg/day** Redness of the eyelids ♂, dry gums, decrease in food consumption, lacrimal gland (hypertrophy of secretory cells), pharynx (ectasia of the ducts and/or alveoli of

Study ID GLP status Duration	Species N	Achieved dose/ (mg/kg/day) Route Formulation MMAD range	NOAEL (mg/kg/ day)	Major findings
				the submucosal glands accompanied by minimal inflammation in the ducts of the submucosal pharyngeal glands) **Recovery**: Mild increases in body weight and absolute body weight gain of animals previously treated at 0.33 mg/kg/day.

DRF, dose-range finding

Genomic analysis (Study 0580297)

The major treatment effect on gene expression following NVA237 treatment of rats for 13 and 26-weeks was a reversible increase in expression of genes related to xenobiotic metabolism (Cyp3a2a) as well as to the bronchial mucosa. The changes in mucosa associated genes were localized in the terminal and respiratory bronchioles, corresponding to the site of morphological change reported by histopathology (hypertrophy of the bronchioloalveolar junction). They comprised genes expressed by associated to mucus/Clara cells. The increase in mRNA expression of the mucus/Clara cells signature was dose dependant, already visible after 3 months of treatment, not stronger after 6 months of treatment and fully recoverable after 4 weeks of recovery. No signs of inflammation could be detected at the molecular level.

Repeat-dose inhalation toxicity studies were conducted in Wistar rats and Beagle dogs with treatment durations of up to 26- and 39-weeks, respectively. The studies were performed using dry powder formulations containing considerably higher levels of glycopyrronium (2-8%), magnesium stearate (0.25-1%) and lactose monohydrate (91-97.75%) than applied clinically. Moreover, the applied mass median aerodynamic diameters were of a size allowing inhalation into the lung. Generally, the findings made could either be ascribed the muscarinic anticholinergic mode of action of glycopyrronium or the local irritation of the airways caused by prolonged inhalation exposure. High safety margins were obtained. Hence, the no observed adverse effect levels (NOAELs) were established in rats and dogs at AUC exposures at least 22-fold and 10-fold higher, respectively, than is observed clinically at a therapeutic dose of 50 µg/day.

As a result of the pharmacodynamic action of glycopyrronium, mydriasis, reduced excretion from exocrine glands and tachycardia were observed in the repeat-dose toxicity studies. Hence, dry oral mucosa or gums, reduced lacrimal gland secretions, hypertrophy of the salivary or lacrimal glands and mild inflammation, dilation of the ducts and/or alveoli of the sub mucosal glands in the pharynx were apparent during the 1-, 4- or 39-week toxicity studies in dogs. Hypertrophy or atrophy of the salivary or lacrimal glands were also observed during a 4-week toxicity study in rats whilst increased porphyrin deposition was recorded in the Harderian glands during 4- and 26-week toxicity studies in rats. Reduced food intake, reduced body weight gain and increased water intake in rats and dry mouth and reduced food intake in dogs were most likely caused by the reduced palatability of the diet. Moreover, the red eyeballs, red eye lids and ocular opacities observed in dogs are most likely the result of the treatment-related reduction in lacrimal gland secretion.

Tachycardia was recorded in dogs at doses ≥0.077 mg/kg/day which gives rise to an AUC based safety margin of 16 to 21-fold in male and female dogs, respectively). This finding is most likely the results of

an exaggerated pharmacodynamic effect on the cardiovascular system since glycopyrronium will reduce the parasympathetic effect on the heart.

Changes in the respiratory tract were evident at all dose levels in the rat repeat-dose toxicity studies. The changes in the larynx consisted of squamous metaplasia, hyperplasia and keratosis accompanied by inflammation in the sub mucosa which was necrotizing in males exposed to 1.3 mg/kg/day for 4-weeks. Moreover, hyaline inclusions and degeneration of the olfactory respiratory epithelium were observed. Based on gene expression analysis, the epithelial hypertrophy noted at the bronchiolalveolar junction appears to be correlated with Clara cells. Similar findings were not made in the respiratory tract of dogs. The innate sensitivity of the upper respiratory tract of rodents to the pathologic effects of inhaled compounds is a well-recognized phenomenon and is probably related to differences in airflow dynamics as well as regional epithelial sensitivity in comparison with non-rodents and humans. Moreover, taking the estimated deposited mass and lung weight into consideration, the local lung exposure at the NOAELs established in the rat studies were 24 to 194-fold higher than that anticipated in humans at the proposed therapeutic dose. Hence, the observed changes in the respiratory tract of rats do not represent a clinical risk.

Cases of glycopyrronium contamination of plasma samples collected from control animals were observed in the pivotal repeat-dose toxicity studies (0580297, 0670548) as well as in the carcinogenicity studies (0670435, 0770668), the study on fertility and early embryonic development (0870596) and the study on embryo-foetal development rabbits (0870597). However, due to the relatively low incidence and the low level of contamination (representing up to 27% of the C_{max} in the lowest dose group), it is considered unlikely that these findings would impact the validity of the studies.

Genotoxicity

The results from the genotoxicity studies are given in the table below.

Type of test/study ID/GLP	Test system	Concentration range/ Metabolising system	Results
Gene mutations in bacteria/0225012/GLP	Salmonella strains TA98, TA100, TA1535, TA1537, TA102	1.6 to 5000 µg/plate +/- S9	**Negative** Toxicity observed following introduction of a S9 pre-incubation step
Gene mutations in mammalian cells/0225013/GLP	Cultured human peripheral blood lymphocytes	2039 to 3983 µg/mL (10 mM) +/- S9	**Negative** Up to 37% mitotic inhibition was seen at the highest dose
Chromosomal aberrations in vivo/0225014/GLP	Wistar rat (6 males/group), micronuclei in bone marrow	250, 500, 1000 mg/kg/day PO for two days*	**Negative** No toxicity to the bone marrow. Mean plasma C_{max} of 4800 ng/ml

**animals were sampled 24 hours following the last dosing*

Glycopyrronium was neither induced gene mutations in bacteria (Ames test), gene mutations in mammalian cells *in vitro* (human peripheral lymphocyte test) or chromosomal aberrations in vivo (rat bone marrow micronucleus test).

Although no exposure to the bone marrow was observed in the Whole-body autoradiography distribution studies conducted in rats following PO administration, it is believed that the bone marrow in the rats in the in vivo micronucleus studies have been sufficiently exposure (as systemic exposure was confirmed and as the bone marrow is highly vascularised). Furthermore, no significant increase in

tumour incidences were observed in the carcinogenicity study conducted in a transgenic mice model (i.e., rasH2 mice); a model which is sensitive to both genotoxic and non-genotoxic human carcinogens.

Carcinogenicity

Carcinogenicity testing comprised a 104-week study in rats and a 26-week study in CByB6F1-Tg (HRAS)2Jic transgenic mice.

Long-term studies

An overview of the 104-week carcinogenicity study in rats is given in the table below.

Study ID /GLP	Dose (mg/kg/day) /Route /Formulation MMAD range	Exposure (AUC/ng.h/mL)	Species/No. of animals	Major findings
0670435/ GLP	Air control 1, air control 2, vehicle, 0.06, 0.17, 0.45 / inhalation MMAD: 2.3-2.5 µm	Low-dose: 8.2, Mid-dose: 22.2 High-dose: 36.5	Wistar rats/ 56-59/sex/group	≥ 0.06: Lens (opacities), nasal cavity (eosinophilic globules in olfactory epithelium, goblet cell hypertrophy/hyperplasia, squamous metaplasia of the respiratory epithelium, respiratory epithelium hyperplasia ♂), larynx (squamous metaplasia), bronchioloalveolar junction (increased incidence of foci or aggregations of alveolar macrophages, epithelial hypertrophy) ≥ 0.17: Reduced body weight gain 0.45: Decreased food consumption, nasal cavity (respiratory epithelium hyperplasia ♀)

On comparison of each of the three control groups, both individually and combined, to the three treated groups by Peto Trend test for endometrial stromal polyp and the combination of endometrial stromal polyp plus endometrial stromal sarcoma, no statistically significant increases were observed except for endometrial stromal polyp when one of three control groups (air control group 2) was compared to the treated groups. When pair wise comparisons were made for the same data sets, none of the groups showed any statistical significance. Based on these statistical results, none of these variations in the incidences of endometrial stromal polyp and endometrial stromal polyp plus endometrial stromal sarcoma were considered to be treatment related. Further examination of the actual incidences of endometrial tumours against background data generated for control animals from comparable carcinogenicity studies using the same strain of animals in the same laboratory indicated that the spontaneous incidence varies from 6% to 11.6% with a mean of 8.43%. In this study, the spontaneous incidences in the control groups were 2%, 4% and 12%, for which 2% and 4% were deemed to be atypically low.

At week 52, the mean plasma AUC0-24 values were 8.2, 22.2 and 36.5 ng.h/mL in the low, mid and high-dose group, respectively. Similarly, the mean C_{max} values were 2.1, 5.7 and 11.9 ng/mL in the low, mid and high-dose group, respectively.

All samples from control groups were analyzed and no concentrations above LLOQ (0.100 ng/mL) were measured in samples from air control group 2 and vehicle control group 3. Three out 21 samples of the air control group 1 had concentrations above LLOQ. These concentrations ranged from 0.333 to 0.974 ng/mL and represent less than 17% on day 1 and about 43% in week 52 of the corresponding mean C_{max} of the low dose. This was considered to have had no impact on the interpretation of the toxicokinetic analyses or conclusions.

No treatment-related neoplastic findings were identified in a 104-week rat inhalation carcinogenicity study at glycopyrronium plasma exposure levels of up to 79-fold higher than is observed in patients inhaling 50 µg/day. In the uterus, imbalances in the incidence of benign endometrial polyps were recorded between control and treated groups. However, the slightly increased incidence of benign endometrial polyps observed at the highest dose level did not exceed the range of historical control incidences and further statistical analysis demonstrated that the increase in incidence was not statistically significant. Altogether, the slightly increased incidence of benign endometrial polyps is most likely of no clinical relevance.

Short or medium-term studies

An overview of the 26-week carcinogenicity study in wild-type and CByB6F1-Tg (HRAS)2Jic transgenic mice is given in the table below. Glycopyrronium bromide was formulated in deionized water for oral administration. A positive control group was applied which received a single IP injection of 75 mg/kg N-methyl-N-nitrosourea (MNU) on study day 1. As expected, the MNU-treated transgenic mice developed multicentric lymphoma and an increased incidence of neoplastic changes in a variety of tissues in both sexes. However, NVA237 treatment neither increased the incidence of neoplastic findings in transgenic mice nor in wild-type mice.

Overview of the 26-week carcinogenicity study conducted in wild-type and CByB6F1-Tg (HRAS)2Jic transgenic mice.

Study ID /GLP	Dose (mg/kg/day) /Route	NVA237 Exposure* (AUC/ng.h/mL)	Species/No. of animals	Major findings
0770668/ GLP	Tg males: Vehicle, 10, 25, 75 /oral gavage Tg females: Vehicle, 10, 30, 100/ oral gavage WT mice: vehicle, 75 (males), 100 (females)	Tg males: 33.1 Tg females: 24.7 WT males: 75.6 WT females: 15.3	Wild-type and CByB6F1-Tg (HRAS)2Jic transgenic mice /25/sex/group	**Tg males:** ≥ 10: Forestomach (epithelial hyperplasia and hyperkeratosis at the limiting ridge, mixed cell inflammation) ≥ 25: reduced body weight gain 75: hunched posture, reduced food consumption **Wt males:** 75: Reduced body weight gain, reduced food consumption **Tg females:** ≥ 10: Forestomach (epithelial hyperplasia and hyperkeratosis at the limiting ridge) 100: hunched posture, reduced food consumption, reduced body weight gain **Wt females:** 100: Reduced body weight gain, reduced food consumption

**Based on toxicokinetic data obtained in study week 22. WT, wild-type; Tg, transgenic.*

NVA237 was not quantifiable in plasma for many animals at the doses of 10, 25, and 30 mg/kg/day as the concentrations were below the LLOQ of 0.100 ng/mL. However, according to the measured concentrations of the NVA237 metabolite CJL603 in plasma, all animals received NVA237. For unchanged NVA237, toxicokinetic parameters were only determined at doses of 75 mg/kg/day (male) and 100 mg/kg/day (female) due to the few quantifiable data points at lower doses. For CJL603 toxicokinetic parameters were determined at all dose levels.

None of the control specimens contained measurable concentration of NVA237. The metabolite CJL603 was detected in two control samples at concentrations of 0.321 ng/mL and 1.83 ng/mL respectively. The two concentrations obtained in the control animals represented only 0.03% and 0.15% of the mean Cmax obtained in the low dose female group and, therefore, do not impact the interpretation of the toxicokinetic results.

In a 26-week oral carcinogenicity study, glycopyrronium treatment did not increase the incidence of neoplastic findings in CByB6F1-Tg (HRAS)2Jic transgenic mice at plasma exposure levels (AUC) up to 50-fold higher than is observed in patients receiving the recommended daily dose.

Reproduction Toxicity

The results from the reproductive and developmental toxicity studies are summarized in the table below.

Overview of the reproductive and developmental studies conducted with NVA237.

Study type/ Study ID / GLP	Species; Number/ group	Route; dose (mg/kg/day)	Dosing period	Major findings	NOAEL (mg/kg)/ safety margin)
0870596/Male fertility/GLP	Wistar rats; 25/group	SC; vehicle, 0.15, 0.5, 1.5	4-weeks prior to mating until SD 50-53	No effect on male fertility parameters	1.5/894-fold
0870596/Female fertility/GLP	Wistar rats; 25/group	SC; vehicle, 0.15, 0.5, 1.5	2-weeks prior to mating until GD6	1.5 mg/kg: ↓ corpora lutea and implantation sites	0.5/162-fold
Embryo-fœtal development/ 0680006/GLP	Wistar rats; 22 dams/ group	Inhalation; air control, vehicle, 0.09, 0.54, 3.05	GD6-GD17	No effect on embryo-foetal development	F0: 0.54/114-fold F1: 3.05/668-fold
DRF Embryo-fœtal development /0680005/GLP	NZW rabbits; 5 females /group	Inhalation; vehicle control, 0.08, 0.56, 1.92, 3.6	GD7-GD19	No effect on embryo-foetal development	F0: 0.56/192-fold F1: 3.6/1730-fold
DRF Embryo-fœtal development /0870597/GLP	NZW rabbits; 20 females/ Group	Inhalation; vehicle control, 0.4, 1.3, 3.5	GD7-GD19	No effect on embryo-foetal development	F0: <0.4/<58-fold F1: 3.5/254-fold
Peri & postnatal/0870598/GLP	Wistar rats; 24 dams/ group	SC; vehicle, 0.15, 0.5, 1.5	GD6-Day 21 to 23 post-partum	1.5 mg/kg: ↓ pup weight	F0: 0.5* F1: 0.5 *

**No toxicokinetic data available. DRF, dose-range finding; GD, gestation day; NZW, New Zealand White; SD, study day*

The MMAD values obtained in the pivotal inhalation studies varied from 1.7 to 2.9 µm hence the particle sizes were respirable to rats. Moreover, the test article applied in the inhalation studies consisted of 8% NVA237 salt form, 1% magnesium stearate and 91% lactose monohydrate. The described doses represent NVA237 in its free base form.

No effects on male rat fertility parameters (including sperm counts and sperm motility) were noted at plasma exposure levels (AUC) up to 895-fold higher than is observed clinically at therapeutic doses. Decreases in the number of corpora lutea and implantation sites were observed females with a NOAEL of 0.5 mg/kg/day. This gives rise to an AUC based safety margin of approximately 160-fold. Overall, it is considered unlikely that treatment with NVA237 will affect fertility in humans at therapeutic doses (50 µg daily).

No effects on embryo-foetal development were observed in pregnant rats exposed to glycopyrronium via inhalation during gestation days 6 to 17 and in pregnant rabbits inhaling glycopyrronium during gestation days 7 through 19. The maximal plasma exposures (AUC) achieved in the pregnant rats and rabbits were around 670- and 250-fold higher than is observed in humans at the maximal recommended daily dose. Furthermore, it should be underlined that glycopyrronium is unlikely to have reached significant concentrations in the foetuses. Nevertheless, this also seems to be the case in humans.

Pre- and postnatal development was not affected in a study applying SC glycopyrronium dosing of pregnant rats. Toxicokinetic evaluations were not performed however based on the data from the rat SC fertility study; it is likely that the plasma exposure was at least 100-fold higher than is observed in humans at the recommended daily dose.

Toxicokinetic data

The listed toxicokinetic parameters listed in the table below are derived from NVA237 plasma exposure data obtained on or close to the last day of dosing.

Overview of the NVA237 plasma exposures (AUC) obtained in the conducted repeat-dose toxicity studies.

Study	Achieved dose (mg/kg/day)	AUC (ng.h/mL)		Cmax (ng/mL)		Animal:human exposure margin AUC		Animal human exposure margin Cmax	
		♂	♀	♂	♀	♂	♀	♂	♀
0848192	0.08	43[a]	30.1[a]	38.3	16.6	93	65	231	100
4-wks	**0.49**	45.4[a]	52.6[a]	15.0	25.3	98	113	90	152
rat	3.39	250[a]	186.8[a]	118.2	104.1	539	403	712	627
0580297	**0.07**	10.1	17.5	2.0	1.9	22	38	12	11
26-wks	0.54	55	68.1	10.5	16.1	119	147	63	97
rat	3.98	353	315	128	102	761	679	771	614
0852241	**0.024**	5.7[b]	6.9[b]	2.3	3.5	12	15	14	21
4-wks	0.077	15.6[b]	20.8[b]	7.8	11.8	34	45	47	71
dog	0.25	64.5[b]	70[b]	31.3	39.9	139	151	189	240
0670548	**0.02**	4.6	4.6	0.9	1.5	10	10	5	9
39-wks	0.09	21.3	33.6	4.1	8.8	46	72	25	53
dog	0.27	80.9	32.8	42.1	8.2	174	71	254	49

a, $AUC_{0\text{-}8\,h}$; b, $AUC_{0\text{-}6.5\,h}$; the doses marked with bold represent the NOAEL; exposure multiples are based on 50 µg, multiple dose [Study CNVA237A2103]; C_{max} = 0.166 ng/mL; $AUC_{0\text{-}24h}$ = 0.464 ng·h/mL

During the toxiciokinetic analysis performed as part of the pivotal 26-week repeat-dose toxicity study in rats (0580297), NVA237 was detected in two air control animals (animal number 1543 and 1544). The measured levels were 0.163 and 0.348 ng/mL which represent concentrations 12- and 6-fold below the C_{max} at the lowest dose level (0.09 mg/kg). Due to the low level of contamination, it is considered unlikely that this finding would impact the validity of the study.

Similarly, in the pivotal 39-week dog study (0670548), NVA237 concentrations above LLOQ (0.100 ng/mL) were measured in 4 out of 300 samples collected from air control animals in week 26 and week 39 (concentrations within the range 0.120 ng/mL to 5.99 ng/mL). Moreover, NVA237 concentrations above LLOQ (0.100 ng/mL) were measured in 9 out of 300 vehicle control samples in day 28, week 26 and week 39 samples (concentrations within the range 0.103 ng/mL to 0.727 ng/mL). Since the measured concentrations are close to LLOQ (except in dog 104) and the concentrations in other time points samples of the same animal were measured below the LLOQ, this is considered of having no impact on the interpretation of the TK analysis and conclusions.

Local Tolerance

Local tolerance in the respiratory tract was evaluated during the rat and dog repeated dose toxicity studies that were performed by inhalation administration.

NVA237 (0.2%, 2.4%, 24% (w/v)) was not identified as a sensitizer in the murine Balb/c local lymph node assay (study 0670690, GLP). Local toxicity was observed at the highest dose tested in the form of reddening of the application site (ear skin) from the second day of application and an increase in draining lymph node weights but there was no associated lymph node hypercellularity.

Other toxicity studies

Immunotoxicity

Standard toxicology studies did not reveal any adverse effects on the immune organs. Immune function assessments during a 4-week inhalation toxicity study in rats (Study 848192) confirmed that there were no changes in leukocyte distribution or on the primary immune response to sheep erythrocytes. The lack of immunotoxicity testing was considered acceptable.

Dependence

Preclinical and clinical studies did not indicate any potential for dependence. Specific investigations were therefore not conducted which was considered acceptable.

Metabolites

No toxicity studies were performed with NVA237 metabolites. Based on the pharmacokinetic data provided, this was considered acceptable.

Studies on impurities

There are no drug substance impurities in glycopyrronium bromide used in the NVA237 clinical formulations that exceeded the threshold for toxicological qualification. The presence of methyl bromide and the intermediate NVA237-B3 (544-05) in the drug substance are tested and controlled according to set specifications. Methyl bromide is Ames test positive. It was found at levels below 10 ppm in 14 development batches and the first 4 launch batches of drug substance. This level would result in a maximum daily intake 0.5 ng/day methyl bromide which is far below the threshold for Toxicological Concern of 1.5 µg/day. The intermediate 544-05 is reported to have hallucinogenic effects at oral doses of 2 to 4 mg. It is limited as an unspecified impurity to ≤0.10%, which corresponds to a maximum daily intake of ≤0.05 µg/day for a daily dose of 50 µg or 40000 times less than the dose reported to have a hallucinogenic effect.

The NVA237 formulation degradation product, cyclopentylmandelic acid (CPMA) and its counterpart 542-07 were qualified in genotoxicity assays and a 4-week repeated dose inhalation toxicity study in rats. A batch of NVA237 (glycopyrronium bromide) spiked with 10.8% CPMA and 8% 542-07 was negative in Ames and chromosome aberration tests.

The toxicological profile of NVA237 and NVA237 spiked with degradation products were compared in a 28-day inhalation qualification study in Wistar rats (10/sex/group). The following parameters were evaluated: clinical signs, body weights, food consumption, ophthalmology, haematology, clinical chemistry, urinalysis, toxicokinetics (week 4), gross observations at necropsy for all groups, organ weights and histopathology. Although the aim was to have 0.6 mg/kg/day as the highest dose, the achieved dose levels were 0.16 (spiked), 0.48 (spiked) and 0.7 (pure) mg/kg/day. The body weight gain and food consumption were decreased in males receiving spiked 0.48 mg/kg/day and 0.7 mg/kg/day (pure). Moreover, a decrease in body weight gain was noted in spiked 0.48 mg/kg/day females. Both treatment caused an in creased number of goblet cells in the nasal cavity. However, erosion of the respiratory/olfactory epithelium and haemorrhage was only observed in the 0.48 spiked group with an incidence of 2/10 and 1/10, respectively. Still, these findings were not made in any of the females. On study day 28, the obtained plasma exposure levels (AUC0-24h) were 12.2, 43.6 and 71.1 ng*h/mL in males exposed to 0.16 (spiked), 0.48 (spiked) and 0.7 (pure) mg/kg/day while the corresponding AUC values in females were 9.36, 39.1 and 58.3 ng*h/mL.

Other studies

Formulation excipients

Oral inhalation studies conducted with magnesium stearate alone or a blend of 1% magnesium stearate in lactose in Wistar rats up to 26 weeks or Beagle dogs up to 52 weeks revealed no toxicological or local respiratory tract tolerance issues.

Combination studies with indacaterol

NVA237 inhalation toxicity studies performed in combination with the beta-2 adrenergic agonist indacaterol (QAB149, Onbrez Breezhaler) comprised 2-week studies in rats and dogs (Study 0670546), (Study 0670547) as well as a 13-week study in dogs (Study 0670756) and an embryo foetal development study in rats (Study 0670755). No findings were made in the combination embryo-foetal study in rats. The findings seen in the repeat-dose toxicity studies were similar to those observed in the studies performed with NVA237 and indacaterol alone. There were some indications of a synergistic effect on heart rate in female dogs. Heart rate increases of 36 and 22% were observed 30 minutes following inhalation of NVA237 (0.128 mg/kg) and indacaterol (0.37 mg/kg), respectively, whereas the combination of the two increased the heart rate by 51%. However, no synergistic effect on heart rate was observed in male dogs.

2.3.5. Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) was estimated to 0.00025 µg/L using the default value for the Fpen and a daily dose of 50 µg. Due to the very low maximum daily dose of 50 µg of active pharmaceutical ingredient, intake of glycopyrronium bromide into the environment through patients use is low and the predicted environmental concentration remains well below the trigger level for a Phase II environmental risk assessment.

Screening for persistence, bioaccumulation and toxicity (PBT) is not deemed necessary for glycopyrronium bromide, as judged from the octanol-water partition coefficient (logKow) of -2.1, determined for this drug substance.

Table 1. Summary of main study results

Substance (INN/Invented Name): Glycopyrronium bromide			
CAS-number (if available): 51186-83-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-2.1	Potential PBT: No

Glycopyrronium bromide $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log K_{ow} does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Based on *in vitro* and *in vivo* pharmacodynamic data, there is a clear rationale for the development of glycopyrronium in COPD. Safety pharmacology studies revealed no risk for effects on the core organs at clinically relevant glycopyrronium exposure levels. Based on pharmacokinetic data on absorption, metabolism and excretion, mice and rats are valid animal models. Overall, the findings made in the repeat-dose toxicity studies could either be ascribed the muscarinic anticholinergic mode of action of glycopyrronium or the local irritation of the airways caused by prolonged inhalation exposure. High safety margins were obtained. Hence, the no observed adverse effect levels (NOAELs) were established in rats and dogs at AUC exposures at least 22-fold and 10-fold higher, respectively, than is observed clinically at a therapeutic dose of 50 µg/day. Glycopyrronium was demonstrated to be non-genotoxic in a standard battery of tests and non-carcinogenic in a 104-week inhalation study in rats and in a 26-week study in HRAS transgenic mice. Furthermore, glycopyrronium did not cause significant effects on fertility, embryo-foetal development or pre- and post-natal development. A reduction in corpora lutea and implantation sites were observed in the female fertility study while a reduction in pup weight was seen in the pre- and post-natal study however in both cases, the findings occurred with a more than 100-fold safety margin.

2.3.7. Conclusion on the non-clinical aspects

A full comprehensive non-clinical programme was conducted to support the clinical program. From a non-clinical point of view, there were no issues identified to be followed up as post-authorisation measures.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The following tables are presented (with several overlaps with regards to the studies across the four groups):

- Studies with pharmacokinetic data

- Studies with pharmacodynamic data
- Studies presenting efficacy data
- Datasets and studies used for the safety evaluation

Studies with pharmacokinetic data

Study Code	Short Title	Design Number of subjects (n)	Treatment duration	Relevance for PK (major objectives)
Healthy subjects - NVA237 studies				
NVA237 A2104	Single dose study with 50, 100 and 200 µg NVA237 in Japanese and Caucasians	Randomized, double blind cross over within ethnic group (37)	Single dose	Effect of ethnicity on PK
NVA237 A2105	Renal impairment study with 100 µg NVA237 in subjects with renal impairment and healthy controls	Open label, single dose, parallel groups (30 subjects with mild, moderate, severe or end stage renal impairment) (18 healthy controls)	Single dose	Effect of renal impairment on PK
NVA237 A2108	Absolute bioavailability of 200 µg inhaled NVA237 and comparison with other routes of administration w/wo charcoal	Open label, single dose, 2 part study. Part I used 2 period crossover (10), Part II used a four period two sequence crossover (20)	Single dose	Absolute BAV of inhaled NVA237, contributions of lung and gastrointestinal absorption to systemic exposure
NVA237 A2109	Drug interaction of 100 µg NVA237 with cimetidine	Open label, 2 period, crossover (20)	Single dose	Effect of inhibition of active tubular secretion on PK
Healthy subjects – QVA149 studies				
QVA149 A2101	Comparative PK with QVA149 (100 µg NVA237 and 300 µg indacaterol)	Randomized, open label, single dose, 4 way cross-over (28)	Single dose	PK interaction between NVA237 and indacaterol
QVA149 A2103	Comparative PK with QVA149 (50 µg NVA237 and 110 µg indacaterol)	Randomized, open-label, repeat dose, 3-way cross-over (43)	2 weeks	Supportive PK of NVA237
QVA149 A2106	Comparative PK with QVA149 (50 µg NVA237 and 110 µg indacaterol)	Randomized, open-label, multiple dose, 4-period cross-over (24)	2 weeks	PK interaction between NVA237 and indacaterol
COPD patients				
NVA237 A2103	Pharmacokinetics, safety and PD for inhaled NVA237 (25, 50, 100 and 200 µg) in COPD patients	Randomized, double blind, placebo controlled, multiple dose, parallel group (41)	2 weeks	Dense PK and some PD measurements to explore PK/PD
NVA237 A2303	Efficacy, safety and tolerability of 50 µg o.d. NVA237 in patients with moderate to severe COPD	Randomized, double blind, placebo controlled with open label tiotropium, parallel group (1066)	1 year	Population PK
NVA237 A2304	Efficacy, safety and tolerability of 50 µg o.d. NVA237 in patients with moderate to severe COPD	Randomized, double blind, placebo controlled, parallel group (822)	6 months	Population PK

Studies with pharmacodynamic data

Study Code	Short Title	Design Number of subjects (n)	Treatment duration	Relevance for PD-response
NVA237 A2103	Pharmacokinetics, safety and PD for inhaled NVA237 (25, 50, 100 and 200 µg) in COPD patients	Randomized, double blind, placebo controlled, multiple dose, parallel group (41)	2 weeks	Dense PK and some PD measurements to explore PK/PD
NVA237 A2205	Dose ranging (12.5, 25, 50, 100 µg) for inhaled NVA237 in Japanese and Caucasian patients with stable COPD	Randomized, double blind, placebo and active (open-label tiotropium) controlled, incomplete block cross-over, multiple dose (83)	1 week	Understanding the dose – response profile of NVA237
NVA237 A2206	Four week safety and tolerability of two doses of NVA237 (100 and 200 µg) in patients with moderate to severe COPD	Randomized, double blind placebo controlled, parallel group, multiple dose study (281)	28 days	Understanding PD-effects on heart rate and QT-interval, and the dose–response of NVA237
NVA237 A2207	Bronchodilatory effect of 50 µg inhaled NVA237 in patients with COPD	Randomized, double blind, placebo controlled two period crossover (33)	14 days	Characterization of 24 h bronchodilator effect profile of NVA237
NVA237 A2208	Efficacy and safety of 4 doses of NVA237 (12.5, 25 and 50µg bid and 12.5, 25 , 50 and 100µg od) given once or twice daily in patients with moderate to severe COPD	Randomized, double blind, placebo controlled two period, 8 treatment, balanced incomplete block (388)	28 days	Effects of two different dosing regimen Understanding Dose-response
NVA237 A2303	Efficacy, safety and tolerability of 50 µg o.d. NVA237 in patients with moderate to severe COPD	Randomized, double blind, placebo controlled with open label tiotropium, parallel group (1066)	1 year	Understanding PD-effect profile (serial spirometry subgroup)
NVA237 A2304	Efficacy, safety and tolerability of 50 µg o.d. NVA237 in patients with moderate to severe COPD	Randomized, double blind, placebo controlled, parallel group (822)	6 months	Understanding PD-effect profile (serial spirometry subgroup)
NVA237 A2310	Effects of 50 µg NVA237 on exercise endurance in patients with moderate to severe COPD	Randomized, double blind, placebo controlled, 2-way cross-over (108)	21 days	Understanding the effect of NVA237 on dynamic hyperinflation
NVA237 A2108	Absolute bioavailability of 200 µg inhaled NVA237 and comparison with other routes of administration w/wo charcoal	Open label, single dose, 2 part study. Part I used 2 period crossover (10), Part II used a four period two sequence crossover (20)	Single dose intravenous infusion & oral dose	Multiple exposures after iv dosing allow to explore secondary PD effects

Studies presenting efficacy data

Source of data	Details
Dose-selection trials	A2205, A2206* and A2208: phase II, placebo- and/or active-controlled, double-blind, cross-over/parallel group dose ranging studies
Controlled pivotal trials	A2304 (6 months), and A2303 (1 year) : phase III, large pivotal, placebo-and/or active- controlled, double-blind, parallel-group studies
Other sources of efficacy (small controlled, supportive trials)	A2310: phase III, placebo- controlled, double-blind, cross-over, exercise endurance study A2207: phase II, placebo-controlled, double-blind, two-period cross-over, 24-h dose profiling study
Long-term trials	A2303: large pivotal, placebo and active-controlled, double-blind, parallel-group study of 1 year

Datasets and studies used for the safety evaluation

Dataset	Studies included	Safety evaluations
COPD Major (two phase III studies, plus the NVA237 50 µg o.d. and placebo dose groups from additional studies)	A2303, A2304, A2205, A2207, A2208, A2310	Topics: deaths, SAEs, other significant AEs, all AEs, special safety topics, clinical laboratory results, vital signs, ECGs Subgroups: by age group, sex, race, COPD severity, number of CCV risk factors, baseline steroid use, exposure
COPD Core (two phase III studies, dataset sub-divided into Core 6-month and Core 12-month for safety assessments)	A2303, A2304	Topics: deaths, SAEs, other significant AEs, all AEs, special safety topics, ECG, 24-h Holter Subgroups: by age group, sex, race, COPD severity, number of CCV risk factors, baseline steroid use, exposure
Short-term (all studies with a treatment duration of less than 28 days excluding NVA237 50 µg data)	A2103, A2104, A2108, A2109, A2205, A2206, A2208, QVA149A2101, QVA149A2103, QVA149A2106	Topics: deaths, SAEs, all AEs
All-treated (all studies from the Major and Short-term Safety databases)	A2103, A2104, A2108, A2109, A2205, A2206, A2207, A2208, A2303, A2304, A2310, QVA149A2101, QVA149A2103, QVA149A2106	Topics: deaths, SAEs, all AEs

2.4.2. Pharmacokinetics

Absorption

- Bioavailability

Study A2108 was a randomized, partly double-blind, two-part, study to determine the absolute, oral and inhaled bioavailability of NVA237.

Upon pulmonal administration, NVA237 is readily absorbed with Tmax values around 5 minutes. Mean steady state Cmax and AUC0-24h values following 14 days treatment with 50 ug NVA237 was 166 pg/mL and 464 pg*h/mL. Following repeated once-daily inhalation of NVA237 by patients with COPD, steady-state concentrations were reached within one week of treatment.

Bioavailability studies demonstrated that charcoal blocks absorption of orally administered NVA237. No difference in the time-concentration profile was detectable between pulmonal administration with or

without concomitant administration of charcoal. Absolute bioavailability based on AUCinf values was about 42% following inhalation of 200 ug by the Concept1 device. AUCinf values were obtainable in 12/18 subjects; estimates based on AUClast were lower (32%). This is likely an underestimation due to substantial differences in elimination half-life upon i.v. and pulmonal administration.

Distribution

In vitro blood distribution and plasma protein binding of NVA237 were studied in animals and humans. Distribution to red blood cells was minor in all species. The NVA237 fractions in plasma were independent of the concentration (10 to 10'000 ng/mL) and were approximately 99% in humans. At concentrations of 1 to10 ng/mL, protein binding was between 38% and 41%.

After i.v. dosing, the steady-state volume of distribution (Vss) of NVA237 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, which reflects the much slower elimination after inhalation.

Elimination

NVA237 disappears from the systemic circulation in a multi-phasic manner. After inhalation, the apparent terminal half-life (T1/2) values differed to some extent between studies with means between 13.0 h and 57.2 h. Values around 20 h were obtained in Study A2103 where sampling was limited to 24 or 48 h after dosing. In studies A2105, A2108 and A2109, with PK sampling up to 72 or 96 h after inhalation and using the most sensitive analytical method, mean T1/2 values varied between 32.5 and 57.2 h in healthy volunteers after single inhaled doses of 100 or 200 µg. Using the single and repeated dose data from Study A2103 the effective half-life was calculated from the accumulation of NVA237 at steady state. Mean values of 16 and 22 h were obtained for the effective half-life.

Renal elimination of unchanged NVA237 accounts for about 60-70% of the total clearance of systemically available NVA237, while other elimination routes accounts for about 30-40%. Mean CLr of NVA237 was between 17.4 and 24.4 L/h. CLr is about 2-3 times higher than the reference value of the glomerular filtration rate, and active tubular secretion by MATE1 and OCT2 is contributing to the renal elimination of NVA237.

About 10% of systemic exposure is due to NVA237 being swallowed. Oral bioavailability of NVA237 is 5%. The M9 metabolite was found in similar amounts as unchanged drug in plasma after inhalation but not after intravenous administration. This metabolite is likely formed from swallowed NVA237, and has been demonstrated inactive against all targets tested in vitro. Biliary excretion contributes about 5% to total clearance, while the remaining non-renal elimination is mediated through CYP oxidation, glucuronidation/sulfation and hydrolysis.

In vitro data suggest that several P450 enzymes contribute to the oxidative metabolism of NVA237, the likely most quantitatively important enzyme being CYP2D6. The circulating M9 metabolite is most likely formed by cholinesterase and origins from proportion of swallowed NVA237 upon inhalation. About 30-40% of systemic available NVA237 is subject to metabolism. No specific data on CYP2D6 genotypes are available from the clinical trials performed. Based on a simulation of PK in subjects devoid of hepatic function, an estimated increase in AUC exposure of about 1.5-fold represents this worst-case scenario. This would represent a less likely extreme situation, and it appears unlikely that this exposure be of clinically relevance given the lack of an apparent plasma concentration-adverse event association.

Dose proportionality and time dependencies

In study CNVA237A2104, healthy Caucasian and Japanese volunteers received single inhaled doses of 50, 100 and 200 µg NVA237 in a crossover design in each ethnic group. In Study A2103, parallel groups of patients with COPD received repeated once daily doses of 25, 50, 100 and 200 µg of NVA237 for 14 days.

Dose proportionality with respect to systemic exposure was sufficiently demonstrated in healthy Caucasian and Japanese subjects. Dose proportionality appears demonstrated in patients with COPD. The PK of NVA237 were time independent upon repeated administration of NVA237. Accumulation ratios for AUC were about 1.44 and 1.69 at 100 and 200ug, respectively. The degree of accumulation is modest and given a lack of an apparent relation between exposure and adverse events this is unlikely to be of clinical relevance.

Special populations

Two population PK analyses were conducted by the applicant: one which included data from one phase 2 study (A2103) and two phase 3 studies (A2303 and A2304) in COPD patients and a second one which included data from the phase 2 study in COPD patients (A2103) and a study of the drug in volunteers with renal impairment. There appeared to be a few discrepancies between the results of the two modeling exercises and between the results of the modeling and findings from other analyses. For example, age (independent of renal function) and not renal function was found to be an important determinant of drug exposure in COPD patients, while in the analysis in renal impairment subjects and phase 2 data from COPD patients, renal function was found to be important. However, since the pharmacokinetics of NVA237 for this application mainly is of importance for safety and tolerability, and since this profile is relatively benign, this issue was not considered significant. While no specific data is available in hepatically impaired patients, a clinical significant change in NVA237 exposure due to impaired hepatic function appeared less likely as renal excretion accounts for about 60-70% of total clearance.

Data from a study in patients with varying degrees of renal impairment and a population PK model including data from this specific study and PK data from a study in COPD patients that included subjects with mild and moderate renal impairment appeared consistent. The Applicant concluded that a 50 µg dose is safe in subjects with mild and moderate renal impairment and this was endorsed by the CHMP.

While no specific data is available, a clinical significant change in NVA237 exposure due to impaired hepatic function appears less likely as renal excretion accounts for about 60-70% of total clearance.

Gender had no apparent effect on NVA237 PK.

An increased exposure in terms of AUClast and Cmax of about 40% and 80%, respectively, is demonstrated in Japanese healthy subjects as compared to Caucasian healthy subject. There is no obvious biological plausible explanation for this difference.

By population PK analysis, AUC exposure at steady state was related to body weight. With a body weight below 50 kg, exposure is estimated to increases with about 44%.

Median steady state AUCtau of NVA237 increased by 70% between COPD patients of age 40 to <45 years and 75 to 80 years. When taking patients of age 60 to <65 years as reference, median AUCtau was 27% higher in patients of age 75 to 80 years, and 25% lower in patients of age 40 to <45 years. These differences are unlikely to be of clinical relevance.

No studies were performed in children.

By population PK analysis, AUC exposure at steady state was related to body weight. With a body weight below

Pharmacokinetic interaction studies

In vitro

In vitro inhibition studies demonstrated that NVA237 has little inhibition potential against CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the ATP-binding cassette (ABC) efflux transporters MDR1, MRP2 or MXR, and the solute-carrier (SLC) uptake transporters OCT1 or OCT2. All IC50 or Ki values were substantially higher than the therapeutic Cmax,ss (> 10'000-fold) as well as the estimated Cgut (≥ 20-fold).

In vitro enzyme induction studies in primary human hepatocytes suggested that a clinically relevant induction by NVA237 for of all the enzymes and transporter tested (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, UGT1A1, MDR1 and MRP2) is unlikely. All mRNA as well as activity data suggest that there would be no clinically relevant induction for all the enzymes and transporter tested.

In vivo

OCT2 and MATE

NVA237 is a substrate for the cationic SLC transporter OCT2 (organic cation transporter 2) and MATE1 (multidrug and toxin extrusion protein). Study CNVA237A2109 was performed to assess the clinical significance of inhibition of OTC21 and MATE1 using cimetidine as a model inhibitor. It was an open-label, two-period, crossover study in 20 healthy subjects.

Treatment A (single inhaled dose of NVA237 100 µg) and Treatment B (cimetidine 800 mg b.i.d. for 6 days plus a single inhaled dose of NVA237 100 µg on the fourth day) were given in a two-sequence crossover fashion, separated by a washout period of 7 to 10 days. Cimetidine increased total exposure (AUClast) to NVA237 by 22% and decreased renal clearance by 23%.

NVA237 and indacaterol

Two separate studies in the development of a different medicinal product allows for a quantification of estimation of an interaction between NVA and indacaterol administered by the Concept1 device. The free combination of inhaled NVA237 and inhaled indacaterol maleate, a long-acting beta-2- adrenergic agonist, was compared with inhalation of each drug alone. Study A2101 was a single dose study comparing NVA237 doses of 100 µg and indacaterol doses of 300 µg. Study A2106 was a 14 day repeated dose study comparing NVA237 doses of 50 µg o.d. and indacaterol doses of 150 µg o.d. on Day 14 under steady state conditions of both drugs. In the free combination treatments NVA237 was inhaled first, followed by indacaterol. The data showed that concomitant pulmonal administration of indacaterol does not influence the PK of NVA237.

Based on in vitro studies, the interaction potential of NVA237 appears low. NVA237 does not inhibit or induce drug metabolising enzymes or drug transporters to any meaningful degree. Inhibition of MATE1 and OTC2 by high-dose cimetidine administration increases AUC exposure by 22%, likely by a similar reduction in renal clearance, with no detectable effect on Cmax. This is unlikely to be of clinical relevance. Concomitant pulmonal administration of indacaterol does not influence the PK of NVA237.

Pharmacokinetics using human biomaterials

Based on in vitro studies, the interaction potential of NVA237 appears low. NVA237 does not inhibit or induce drug metabolising enzymes or drug transporters to any meaningful degree.

2.4.3. Pharmacodynamics

Mechanism of action

Parasympathetic nerves are the major bronchoconstrictor neural pathway in airways, and cholinergic tone is the major reversible component in COPD. Stimulation of these nerves results in release of acetylcholine (ACh) that acts at multiple muscarinic receptor subtypes. Of the five known muscarinic receptor subtypes (M1-5), subtypes M1-3 are of relevance in the human lung.

NVA237 is a highly potent muscarinic receptor antagonist of these three receptor subtypes. It demonstrated on average 4- to 5-fold selectivity for the human M3 and M1 over the human M2 receptor in competition binding studies. This selectivity assessment is based on apparent binding affinity constants (pKi values) of 9.60 to 9.81 for M1, 8.70 to 9.25 for M2 and 9.47 to 9.64 for M3 (mean data from three studies). In addition, NVA237 showed faster dissociation form the M2 receptor over the M1 and M3 receptors. The kinetic selectivity (dissociation rates form M2 over M3 receptors) was 9-fold for NVA237 compared to 4-fold for tiotropium. In vitro binding kinetics of NVA237 indirectly suggest that at equi-effective concentrations, NVA237 will reach equilibrium faster than tiotropium, and suggest a more rapid onset of action. This was confirmed in clinical phase II and III studies. Muscarinic agonist-induced bronchoconstriction was markedly reduced by intratracheal installation of GP in rats and this effect was maintained 24 h post-dose, although the potency of GP slightly decreased over this time period.

Primary pharmacology

Bronchodilator effects of anticholinergic drugs are commonly quantified using spirometric endpoints. The most widely used and accepted parameter is FEV_1 as it has the advantage of being the most repeatable lung function parameter and one that measures changes in both obstructive and restrictive types of lung disease. Trough FEV_1 was used as the primary efficacy measure in the primary PD studies and throughout the Phase II/III efficacy studies in the NVA237 development. Trough FEV_1 was defined as the mean of FEV_1 measurements at 23 h 15 min and 23 h 45 min post morning dose. All studies were placebo-controlled, A2205 including tiotropium as active comparator. A cross-over design was chosen in A2205, A2207 and A2208 as within-patient variability in FEV_1 is less than between-patient variability in this patient population. The wash-out periods seem appropriate (A2205/A2208: 7 days, A2207: 7-14 days). Reversibility was generally high. This will be discussed further in the section of Clinical Efficacy.

Study A2205

The study was a phase II randomized, double-blind, placebo-controlled, multicenter, multidose (7 days), 6 treatment, 4 period incomplete block cross-over study to compare the efficacy of 4 doses of NVA237 (12.5, 25, 50 and 100 µg once daily) with 18 µg tiotropium as active comparator in 83 patients with stable COPD (25 Japanese and 58 caucasian). A difference from placebo of 0.120 L in trough FEV_1 was considered to be the minimally clinically important difference for COPD patients.

The primary efficacy analysis was based on the following ANCOVA model: Trough FEV_1 at day 7 = patient effect + treatment effect + period effect + (period) baseline FEV_1 + error. Patients receiving at least one study medication were included in the modified intention to treat population (mITT). Baseline characteristics between the Japanese and non-japanese population was comparable, though the Japanese population was male and older with 88% being older than 65 years compared to 38% in the non-japanese population. 5 of 83 patients discontinued the study, 3 due to adverse events and 2 due to withdrawn consent. 80% of the patients received COPD related medication. The Japanese population

were only treated with long acting medications, whereas the non-japanese population was treated with both short- and long acting medications.

Treatment with NVA237 resulted in a dose-related increase in FEV_1 values beginning 5 minutes after inhalation of the study drug.

The primary endpoint, trough value of FEV_1 at day 7, was comparable to tiotropium 18 µg. The trough FEV_1 was higher than placebo for all strengths as well as for tiotropium, ranging from 0.08, 0.09, 0.13 and 0.14 L for 12.5, 25, 50 and 100 µg NVA237 respectively and 0.13 L for 18 µg tiotropium. The difference was statistically significant.

The study showed that 50 µg once daily was efficacious and safe. Reversibility is generally above 12%. The FEV_1 /FVC is below 0.70 as recommended in guidelines (CPMP/EWP/562/98/Rev.1).

Study A2205 showed a clear dose-response relationship in the range from NVA237 12.5 µg to 100 µg once daily on trough FEV_1. The doses of 50 µg and 100 µg of NVA237 had comparable effect on trough FEV_1 to tiotropium 18µg once daily. NVA237 100 µg once daily did not offer significant advantage over NVA237 50 µg once daily.

Study A2206

Study A2206 was a randomized, double-blind, placebo controlled, parallel group, multi-center study, to assess the safety and tolerability of 28 days treatment with NVA237 (100 or 200 µg once a day) in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD). Even though the efficacy assessment was a secondary parameter, it was shown that the 200 µg dose only offered marginal better effect on FEV_1 than 100 µg. No safety issues were identified. Study A2206 showed that NVA237 100 µg and NVA237 200 µg q.d. were safe and well tolerated.

Study A2207

Study A2207 was a randomized, double-blind, placebo-controlled, multi-center, two-period crossover study to investigate the bronchodilatory effect of 50µg NVA237 inhaled once daily in patients with Chronic Obstructive Pulmonary Disease (COPD).

It was a supportive pharmacodynamic study performed corroborating the once daily dosing in terms of demonstrating a sustained effect through 24 hours. Concomitant medication was permitted in the study as long as this remained stable throughout the study. The medications that were allowed were: cromoglycate, nedocromil, ketotifen in recommended and constant doses and dose regimens. A difference from placebo of 0.120 L in trough FEV_1 was considered to be the minimal important clinical difference for COPD patients. In comparison in Study A2205 the difference of the trough value of FEV_1 at day 7 was 0.13 L.

Study A2207 showed that NVA237 50 µg q.d. was significantly better than placebo, with an improvement in trough FEV_1 after 14 days treatment of 0.154 L. The 24h profile of FEV_1 after NVA237 50 µg q.d. did show a significant benefit over placebo (except for trough FEV_1 at day 7).

Study A2208

Study 2208 investigated once daily (q.d) versus twice daily (b.i.d) regimen. It was a randomized, double-blind, placebo controlled, eight treatments, two-period, balanced incomplete block study. Patients were randomized to one of the 16 sequences to receive two of the eight possible treatments: 12.5, 25 and 50 µg q.d. and b.i.d, 100 µg q.d. or placebo. Each treatment was taken for 28 days with a 7 day washout between each period.

The primary objective was to evaluate incremental doses of NVA237 q.d. and b.i.d. and the effect on trough FEV_1 after 28 days of treatment.

Study A2208 showed a better effect on trough FEV_1 after 28 days of treatment with NVA237 25 µg and 50 µg b.i.d compared to NVA237 50 µg q.d, with a difference of 0.032 L and 0.051 L respectively. The dose of 12.5 µg b.i.d. as well showed a comparable effect to 50 µg q.d.

Study A2310

Study A2310 was a multicenter, randomized, double blind, placebo controlled, two period cross over study to assess the effect of NVA237 50 µg q.d. on exercise endurance in patients with moderate to severe COPD. The treatment period was 21 days at the end of which patients performed a sub-maximal constant load cycle ergometry test (SMETT) to determine their exercise endurance time.

At day 21 there was a difference in endurance time of 89 seconds when compared to placebo. The improvement in exercise endurance was seen already after the first dose, with a difference of 43 seconds compared to placebo. NVA237 had a positive impact on exercise endurance (sub-maximal constant-load cycle ergometry test - SMETT), with an increase in endurance of 89 seconds after 21 days of treatment and the effect on exercise endurance was present already after the first dose (43 sec).

Secondary pharmacology

Study CNVA237A2108

Study A2108 was a two part study in healthy volunteers. Part 1 was a randomized, open-label, two-period, crossover study. Treatment periods were separated by a washout period of 10 to 21 days. Treatments were single oral doses of 400 µg NVA237 (content of eight 50 µg inhalation capsules) administered with and without activated charcoal. Ten subjects were enrolled into this part. The primary objective of Part 1 was to determine the effectiveness of oral activated charcoal in reducing or blocking the gastrointestinal (GI) absorption of NVA237.

Part two of Study A2108 determined the absolute bioavailability of inhaled NVA237 (with and without activated charcoal) compared to intravenous administration of GP and assessed safety and tolerability of the different routes of administration.

Holter monitoring was performed in Part 2 of Study A2108 for the two i.v. treatments and for inhaled NVA237 without charcoal. There is a small decrease in peak heart and mean heart rate under i.v. GP when compared to placebo.

The results of a QTc study showed that a single dose of 400 µg of NVA237 (8 times the projected therapeutic dose of 50 µg) had no 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 whereas the positive control, moxifloxacin showed the expected clinical effect on QTcF interval. The slight bradycardic effect observed in other studies was also observed in this study.

2.4.4. Discussion on clinical pharmacology

NVA237 acts as a competitive antagonist at muscarinic acetylcholine receptors and belong to the class of anti-cholinergics. Injectable and oral formulations are already in use. Other anticholinergics in the treatment of COPD are the short acting ipratropium and the long acting tiotropium.

NVA237 was developed as a once-daily inhalation treatment in patients with moderate to severe chronic obstructive pulmonary disease (COPD), delivered via a single dose dry powder inhaler Concept1. The dose and dosing regimen was selected based on data from phase II studies A2205, A2206 and A2207 which demonstrated that 50 µg once daily (q.d.) was an effective dose compared to

placebo, showed similar efficacy to tiotropium and has a wide therapeutic index of safety. Different dosing regimens (twice daily vs once daily) were compared in study A2208.

In Study A2205, NVA237 showed a clear dose-response relationship from the doses of NVA237 12.5 µg to 100 µg once daily and NVA237 50 µg once daily had a significant and relevant benefit in trough FEV_1 compared to placebo. The effect was comparable to that of tiotropium, which was used as an active comparator in study A2205.

Study A2206 was conducted to demonstrate safety and tolerability with 100 µg and 200 µg NVA237 given for 28 days. Even though the efficacy assessment was a secondary parameter, it was shown that the 200 µg dose only offered marginal better effect on FEV_1 than 100 µg. No safety issues were identified.

Study A2207 showed that NVA237 50 µg q.d. was significantly better than placebo, with an improvement in FEV_1 after 14 days treatment of 0.154 L. The 24h profile of FEV_1 after 50 µg NVA237 did show a significant benefit over placebo (except for trough FEV_1 at day 7). The study also included patients with mild COPD.

Study A2208 showed a better effect on trough FEV_1 after 28 days of treatment with NVA237 25 µg and 50 µg b.i.d., with a difference of 0.032 L and 0.051 L respectively compared to 50 µg q.d. The dose of 12.5 µg b.i.d. as well showed a comparable effect to 50 µg q.d.. Looking at the dose-response curve of trough FEV_1, a twice daily dosing with 50 µg seem to be more beneficial.

The Applicant uses two different minimal clinical relevant differences, 0.120 L in studies A2205 and A2207 (which was prespecified in the protocol) and 0.100 L (not prespecified) in Study A2208. The difference in trough FEV_1 after NVA237 50 µg once daily is 0.109 L. According to study A2208, the NVA237 25 µg twice daily regimen offers a benefit in trough FEV_1 over NVA237 50 µg once daily. In Study A2208, the group receiving NVA237 25 µg twice daily had more severe COPD than the ones treated with NVA237 50 µg once daily. If this difference in severity of COPD has an impact on trough FEV_1, the effect of the twice daily regimen will be underestimated, because the more severe COPD, the less benefit of the treatment.

In Study A2310, NVA237 50 µg once daily compared to placebo had a positive impact on exercise endurance (sub-maximal constant-load cycle ergometry test - SMETT), with an increase in endurance of 89 seconds after 21 days of treatment and the effect on exercise endurance was present already after the first dose (43 sec).

The results of a QTc study showed that a single dose of 400 µg of NVA237 (8 times the projected therapeutic dose of 50 µg) had no 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 whereas the positive control, moxifloxacin showed the expected clinical effect on QTcF interval. The slight bradycardic effect observed in other studies was also observed in this study.

In Study A2206 laboratory values were largely unchanged during the study and no impact from NVA237 on vital signs and ECG was seen. An analysis of Fridericias QTc on day 28 shows no significant increase compared to placebo.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of NVA237 has been sufficiently studied in healthy subjects, in COPD patients and in patients with impaired renal function. Results are generally consistent across trials and study populations. The pharmacodynamics properties are adequate explored. Overall, the clinical pharmacology of NVA237 was sufficiently investigated by the Applicant and there are no outstanding issues.

2.5. Clinical efficacy

The present stand-alone clinical development program comprises 12 clinical studies with 5 phase I clinical studies supplemented with pharmacokinetic data from subsets of patients from two phase III studies (A 2303 and A 2304), 4 phase II dose finding studies and lastly 3 phase III clinical studies, where two are pivotal clinical study on efficacy. A detailed overview of the individual phase II and III studies appears in Table 1 below.

Table 1: Summary of phase II (A2205, A2206, A2207 and A2208) and phase III (A2303, A2304 and A2310) clinical studies of NVA237

Study ID	Study Objective	Number of patients	Treatment Duration	Medication dose/day	Primary Endpoint
A2205	Dose ranging in patients with COPD	83	7 days	Placebo Tiotropium 18 µg o.d. NVA237 12.5 µg o.d., 25 µg o.d., 50 µg od, 100 µg o.d.	Mean Trough FEV_1 at 7 days
A2206	Safety and tolerability	281	28 days	Placebo NVA237 100 µg o.d., 200 µg o.d.	Safety/tolerability of 28 days of treatment with NVA237 100 and 200µg o.d.
A2207	24-h dose profiling study	31	14 days	Placebo NVA237 50 µg od	FEV_1 24-h profile
A2208	Dose ranging in patients with COPD	388	28 days	Placebo NVA237 12.5 µg o.d., 25 µg o.d., 50 µg o.d., 100 µg o.d. NVA237 12.5 µg b.i.d., 25 µg b.i.d., 50 µg b.i.d.	Modeled trough FEV_1 at 28 days
A2303	Long-term efficacy, safety and tolerability of NVA237 in patients with COPD	1066	365 days	Open Label Tiotropium 18 µg o.d. NVA237 50 µg o.d.	Trough FEV_1 at Week 12, TDI* at 26 weeks, SGRQ** at 52 weeks
A2304	Long-term efficacy, safety and tolerability of NVA237 in patients with COPD	822	183 days	Placebo NVA237 50 µg o.d	Trough FEV_1 at Week 12, TDI* and SGRQ** at 26 weeks
A2310	Efficacy of NVA237 in patients with COPD	108	21 days	Placebo NVA237 50 µg o.d.	Exercise endurance after three weeks of treatment

*Breathlessness measured using the Transition Dyspnea Index (TDI)

** Health status measured using the total score of the St George's Respiratory Questionnaire (SGRQ)

2.5.1. Dose response studies

A2205

The study was a placebo controlled study with an active control arm, of an incomplete block cross-over design. 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 µg), NVA237 12.5, 25, 50 and 100 µg. Each patient was randomised to 4/6 1 week treatment periods in an open block design.

The presence of a dose response effect was evaluated for statistical significance using two sided hypothesis testing based on the following four main contrasts for this study:

- NVA237 12.5 µg versus placebo
- NVA237 25 µg versus placebo
- NVA237 50 µg versus placebo
- NVA237 100 µg versus placebo

The primary objective was to evaluate the bronchodilatory efficacy of NVA237 in patients with stable COPD in terms of trough FEV_1 (mean of 23h 15min and 23h 45min post dose) following 7 days of treatment, by comparing four doses of NVA237 (12.5, 25, 50 and 100 µg o.d.) with placebo delivered by the Single Dose Dry Powder Inhaler (SDDPI). The secondary objective was to determine the efficacy of NVA237 in terms of trough FEV_1 on Day 1 and a number of different FEV_1 and FVC measurements. No measurements of disease activity or quality of life were made.

Patients included in the study were:

- Male or female adults aged ≥40 years, who signed an Informed Consent Form prior to initiation of any study-related procedure.
- Patients with moderate to severe COPD according to the GOLD Guidelines.
- Patients who had a smoking history of at least 10 pack years. Ten pack-years is defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.
- Patients with a post-bronchodilator FEV_1 ≥30% and < 80% of the predicted normal, and post-bronchodilator FEV_1/FVC < 0.7 at Visit 2.

Among several relevant exclusion criteria patients with a history of asthma (indicated by, but not limited to, blood eosinophil count greater than 400/mm3 or onset of symptoms prior to age 40 years) were excluded, but no limit on airway reversibility was used.

A total of 83 patients were included in the analysis study as the modified intent-to-treat population where the per protocol population was 72.

For the primary efficacy variable trough FEV_1 at day 7 the results showed that both the 50 ug and 100 ug NVA237 doses resulted in increases of trough values larger than the minimal relevant clinical effect of 120 ml with increases of 131 and 142 ml respectively. All four doses of NVA237 resulted in significant greater increases in trough FEV_1 than placebo and the 50 ug and 100 ug NVA237 showed results comparable to tiotropium bromide, where the latter showed an increase in trough $FEV_1$of 127 ml.

For the secondary variable post-dose FEV_1 measured successive in the following 24 hours from first dose at day 1 and last dose at day 7 dose response appeared for NVA237 4 hours after inhalation and beyond.

Dose selection was exclusively based on lung function parameters.

The overall conclusion that a dose of 50 ug NVA237 is adequate for a once-daily regimen is justified from the findings of a trough FEV_1 greater than the clinical minimum increase of 120 ml, the observed similar results for the 100 ug dose and for tiotropium. The choice of the 50 µg dose for a once daily dose regimen is considered appropriate since the 100 µg dose is only marginally more efficacious, whereas the 25 µg dose appears considerably less efficacious than the 50 µg dose.

A2206

The primary objective of Study A2206 was tolerability and safety. This study used a three-arm, randomized, double-blind, parallel-group, placebo-controlled, multicenter study design in patients with COPD aged 40 years of age or older. Patients received either NVA237 100 µg, 200 µg or placebo for 28 days.

A total of 92 patients were randomized to NVA237 100 ug and 98 were randomized to NVA237 200 ug q.d. and 91 to placebo and these three groups defined the intent to treat population.

For the main efficacy variable among the secondary objectives the trough FEV_1 after NVA237 100 and 200 ug q.d. were both significantly increased when compared to placebo at Day 1, Day 14 and Day 28. The difference in absolute value between NVA237 100 ug and placebo in trough FEV_1 was a mean of 131 ml (Day 1), 146 mL (Day 14) and 161 mL (Day 28). Likewise the difference in absolute value between NVA237 200 ug and placebo was 146 mL (Day 1), 193 mL (Day 14) and 151 mL (Day 28).

The main results obtained from Study 2206 relate to safety data. With regard to efficacy results (secondary objectives), both doses of 100 and 200 µg increased trough FEV_1 significantly more than placebo, and the absolute increase in trough FEV_1 for both was more than 120 mL when compared to placebo.

A2207

This study was a randomized, double-blind, placebo-controlled, two-period cross-over multicenter trial in patients with mild, moderate or severe COPD. A total of 32 patients were to be randomized into one of two sequences to receive either NVA237 50 µg followed by placebo (Sequence A) or placebo followed by NVA237 50 µg (Sequence B). The study consisted of a screening period (performed between 21 to 2 days prior to first dose) and two treatment periods separated by a 7 to 14 day washout. Each period consisted of a baseline on Day -1 of each period and 14 days of treatment followed by a study completion evaluation on Day 15 of period 2.

The primary objective was to investigate the bronchodilatory efficacy of 50 µg NVA237 over 24 hours following 14 days treatment as compared to placebo in patients with mild, moderate or severe (Stage I-III) stable COPD. The primary efficacy variable was the standardized FEV_1 AUC0-24h, i.e. AUC0-24h/24, following 14 days of treatment, where 24h was understood as the 23h45 assessment.

The 33 patients enrolled had a mean age of 60.5 years, a mean duration of COPD of 4.8 years, a mean FEV_1 reversibility of 21.8 % (SD = 16.0), and a mean baseline FEV_1 pre-ipratropium of 1.79 L.

For the primary variable on efficacy, the FEV_1 AUC0-24 h (L) on Day 14 active treatment with NVA237 50 ug q.d. resulted in a mean value of 1.827 where placebo had a mean of 1.664 with a resulting difference between active and placebo of 0.163 L.

From the curve on mean FEV_1 in 24 hours the largest difference to placebo occurred 1 hour post dosing, the difference levelled off the next 1 to 8 hours and then increased to a second peak at 13 hours post dosing and the significant difference to placebo was sustained for 24 hours.

The study is a small but very detailed study on the clinical profile of improvements in lung function in 24 hours post dosing of NVA237 50 ug once daily at Day 7 and 14 of continuous treatment, where 31 adult patients with COPD participated. The patients stayed in the single participating clinic where they were followed with lung function measurements for more than 24 hours. The main conclusion of a sustained and consistent increase in several lung function parameters compared to placebo over 24 hours is solid and the difference in trough FEV_1 24 hours post dosing of 0.163 L is clinically relevant.

A2208

The study was a double-blind, randomized, dose finding trial utilizing an eight-treatment, two period (29 days each), balanced incomplete block design where the doses were delivered once or twice daily. Patients were randomized to 16 independent sequences that resulted from this design. The treatments studied were q.d. (12.5 µg q.d., 25 µg q.d., 50 µg q.d and 100 µg q.d.), and b.i.d (12.5 µg b.i.d., 25 µg b.i.d., and 50 µg b.i.d), and placebo administered over 28 days each. As the study design incorporated a twice dosing regimen, all patients took study medication (active or placebo) in the morning and in the evening.

The primary objective was to evaluate the relationship of incremental doses of NVA237 q.d. and b.i.d. and their effect on trough FEV_1 after 28 days of treatment, as defined by the percentage of the maximal effect that each dose achieves in relation to the maximal effect of NVA237. (Trough was defined as the mean of FEV_1 measurements at 23 h 15 min and 23 h 45 min post morning dose).

A key secondary objective was to evaluate the magnitude of any difference of effect on trough FEV_1 after 28 days of treatment between the same total daily doses of NVA237 by comparing once daily and twice daily dosing.

To be randomised to the study at visit 3 the patients had to fulfil the inclusion criteria:

- Male or female adults ≥40 years of age, who had signed an Informed Consent Form prior to initiation of any study-related procedure.
- Patients with moderate to severe stable COPD (Stage II or Stage III) according to the GOLD Guidelines 2008.
- Current or ex-smokers who had a smoking history of at least 10 pack years. (Ten pack years were defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
- Patients with a post-bronchodilator FEV_1 ≥30% and < 80% of the predicted normal, and post-bronchodilator FEV_1/FVC < 0.7 at Visit 2 (Day -8). (Post refers to 45 mins after inhalation of 84 µg ipratropium bromide)
- Symptomatic patients, according to daily electronic diary data between Visit 2 (Day -8) and Visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3.

At the second screening visit an anti-cholinergic reversibility test was performed.

A dose-response relationship on trough FEV_1 was observed in both the once daily and twice daily dosing regimens, where the increase in trough FEV_1 compared to placebo was 0.109 L for 50 µg once daily and 0.137 L for 100 ug once daily and 0.141 L for 25 ug twice daily compared to 0.160 for 50 µg twice daily. When compared as 50 µg once daily with 50 µg twice daily the former results in an increase of 0.109 L above placebo while the latter results in an increase of 0.160 L compared to

placebo, where the 90% confidence interval for the latter is 0.135 to 0.181 and for the former is 0.083 to 0.135.

When comparing the primary endpoint for the different regimens at Day 28, the twice daily dosing provided greater improvement in trough FEV_1 compared to placebo than the once daily dosing for the total daily doses of 25 µg, 50 µg and 100 µg. For the 50 µg once daily the treatment difference compared to placebo was 0.109 L compared to 0.141 L for 25 µg twice daily. From the confidence interval of the observed differences the 90% CI on the differences does not contain 0, where for example, the difference between 50 ug once daily and 25 ug twice daily is 0.032 L with CI 0.012 – 0.046 L and thus statistically significantly ($p < 0.05$) different. The same result is obtained when comparing 25 µg once daily with 12.5 µg twice daily and 100 µg once daily to 50 µg twice daily.

Study A2208 confirms that NVA237 50 µg and 100 µg once daily results in comparable effects on the primary objective trough FEV_1 with increases of 0.109 L and 0.137 L respectively, confirming the conclusion from Study A2205. When the same total daily dose given once daily is compared to twice daily, the latter results in significant improvement in the primary variable, trough FEV_1 24 hours post dosing, primarily reflecting the effect of the second dose of NVA237 25 µg administered 12 hours prior to measurements. The difference in absolute value over placebo is 0.109 L for 50 µg q.d. and 0.141 L for 25 µg b.i.d.

The once daily regimen has a clearly demonstrated efficacy and offers a benefit regarding patient compliance. However, some limited data suggest that inhaling 25 µg twice daily instead of 50 µg once daily may possibly be a better dose schedule in terms of safety and efficacy. In order to address this, the CHMP requested a post-authorisation clinical study to further characterise the optimal dosing schedule for NVA237. "Optimal dosing schedule" was considered as important missing information at the time of Opinion and should be added in the RMP.

As for Study 2205 the exclusion criteria in relation to asthma were weak and did not include strict reversibility criteria in relation to lung function and indeed again a significant degree of reversibility was observed on day 1 in relation to dosing of NVA237.

2.5.2. Main studies

Table 2: Summary of the two phase III studies (A2303 and A2304) on NVA237.

Study ID	Study Objective	Number of patients	Treatment Duration	Medication dose/day	Primary Endpoint
A2303	Long-term efficacy, safety and tolerability of NVA237 in patients with COPD	1066	365 days	Open Label Tiotropium 18 µg o.d. NVA237 50 µg o.d.	Trough FEV_1 at Week 12, TDI* at 26 weeks, SGRQ** at 52 weeks
A2304	Long-term efficacy, safety and tolerability of NVA237 in patients with COPD	822	183 days	Placebo NVA237 50 µg o.d	Trough FEV_1 at Week 12, TDI* and SGRQ** at 26 weeks

*Breathlessness measured using the Transition Dyspnoea Index (TDI)

** Health status measured using the total score of the St George's Respiratory Questionnaire (SGRQ)

The two pivotal studies, A2303 and A2304, were very similar, and they are summarised jointly with reference to each study when necessary.

- Study A2303: 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.

- Study A2304: 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.

Methods

Study Participants

Both pivotal studies aimed to include the same target population of adult males and females (age 40 years and over) with a clinical diagnosis of stable moderate to severe COPD (GOLD guidelines 2008) and a smoking history of at least 10 years. In both studies the individual investigator was to ensure that all patients who met the inclusion and exclusion criteria actually were offered enrolment in the study. Patients were selected at visit 1 and 2 with randomisation at visit 3.

Both studies had exactly the same inclusion and exclusion criteria:

Inclusion criteria

- Male or female adults aged ≥ 40 years, who signed an Informed Consent Form prior to initiation of any study-related procedure.
- Patients with moderate to severe stable COPD (Stage II or Stage III) according to the (GOLD guidelines 2008).
- Current or ex-smokers who had a smoking history of at least 10 pack years. (Ten pack years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
- Patients with a post-bronchodilator FEV_1≥ 30% and < 80% of the predicted normal, and post-bronchodilator FEV_1/FVC < 0.7 at Visit 2 (day -14)
- Patients, according to daily electronic diary data between Visit 2 (-14) and Visit 3 (day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3

Exclusion criteria

Among several relevant exclusion criteria, patients with a history of asthma (indicated by, but not limited to, blood eosinophil count greater than 400/mm3 or onset of symptoms prior to age 40 years) were excluded, but no limits on airway reversibility were used.

Treatments

A2303 *(treatment duration 52 weeks)*

The study treatments were:

- Investigational drug - NVA237A 50 µg delivered via a single-dose dry powder inhaler (SDDPI)
- Matched placebo delivered via SDDPI
- Open-label tiotropium 18 µg o.d. delivered via the Handihaler

A2304 *(treatment duration 26 weeks)*

The study treatments were:

- Investigational drug - NVA237A 50 µg delivered via a single-dose dry powder inhaler (SDDPI).
- Matched placebo delivered via SDDPI.

Objectives

The primary objective was identical in the two studies: to confirm that NVA237 50 µg o.d. (delivered via a SDDPI) vs. placebo significantly increases trough FEV_1 (defined as mean evaluation at 23 h 15 min and 23 h 45 min post dose) following 12 weeks of treatment in patients with moderate to severe COPD (GOLD guidelines 2008).

The key secondary objectives were similar but with different observational length in the two studies:

- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on breathlessness measured using the Transition Dyspnoea Index (TDI) after 26 (both A2304 and A2303) weeks treatment.
- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on the health status by measuring the total score of the St George's Respiratory Questionnaire (SGRQ) after 26 (A2304) or 52 (A2303) weeks treatment.

The important secondary objectives were similar but with different observational length in the two studies:

- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on time to first COPD exacerbation during 26 (A2304) or 52 (A2303) weeks treatment.
- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on daily rescue medication use (number of puffs) over 26 (A2304) or 52 (A2303) weeks.

Additional secondary efficacy objectives were:

- To evaluate the effect of NVA237 (50 µg o.d.) on lung function (FEV_1, Forced Vital Capacity (FVC)) at all time points (including FEV_1 AUC5min-12h and FEV_1 AUC5min-24h in a subset of patients, as compared with placebo, with respect to the early response, approximate peak response and trough response (AUC = area under the curve). The subset of patients differed in the two studies since Study A2303 intended a subset of 330 patients: approximately 166 NVA237 patients, 82 placebo and 82 tiotropium, and Study A2304 intended a subset of 250 patients: approximately 167 NVA237 and 83 placebo.
- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on rate of COPD exacerbations during the 26 (A2304) or 52 (A2303) week randomized treatment period.
- To evaluate the effect of NVA237 (50 µg o.d.) vs. placebo on other COPD symptoms collected via patient diary over the 26 (A2304) or 52 (A2303) week randomized treatment period.

Outcomes/endpoints

Primary endpoint: Trough FEV_1 (at 23 h 15 min and 23 h 45 min post dose) after 12 weeks (visit 9) of treatment. The same lung function measurement was repeated at visits 4, 9, 13 and 18 (the latter only in A2303). Unless otherwise stated, trough FEV_1 assessments excluded values taken within 6 hours of rescue medication use or 7 days of systemic corticosteroid use. The baseline FEV_1 measurement was

defined as the average of the values taken at -45 and -15 min prior to first dose of study drug at Day 1.

If trough FEV_1 was missing, the pre-dose trough FEV_1 (the mean of 45 and 15 min pre-dose values) was carried forward from the last non missing visit as long as the visit was not prior to Day 15 or from a premature discontinuation visit or an unscheduled visit. Sensitivity analyses (not using LOCF and using the repeated measures approach) have confirmed that the LOCF imputation method was sufficiently conservative.

Secondary endpoints: TDI dyspnoea index, SGRQ score, time to first exacerbation of COPD, number of exacerbations, use of rescue medication, 24-hour FEV_1 profile, symptoms of COPD collected via patient diary.

TDI index

Patients were interviewed by an independent, trained assessor who graded the degree of impairment due to dyspnoea at Visit 3 (baseline dyspnoea index (BDI)) and at Visits 8, 12 and 17 (A2303 only) as the transitional dyspnoea index (TDI). The same assessor completed all the BDI/TDI assessments for an individual patient.

SGRQ score

The St George's Respiratory Questionnaire (SGRQ) was used to provide a score on the health related quality of life. The SGRQ was always completed before any other assessments were made to avoid influencing the responses. The SGRQ scores in three components, where the lowest score is 0 and the highest score 100 and the minimal clinically important difference is 4.

COPD exacerbations

The time to first acute exacerbation of COPD and the number of exacerbations in the observational period was registered from the following definition of exacerbation:

- Worsening of two or more of the following major symptoms for at least 2 consecutive days:
    - dyspnoea
    - sputum volume
    - sputum purulence

Or:

- Worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:
    - sore throat
    - colds (nasal discharge and/or nasal congestion)
    - fever without other cause
    - increased cough
    - increased wheeze

If a patient experienced a COPD exacerbation he/she was treated as deemed appropriate by the investigator.

Furthermore the severity of moderate and severe exacerbations was defined as:

- moderate severity if treatment with systemic corticosteroids and/or antibiotic was required

- severe severity if treatment for moderate severity (listed above) and hospitalisation was required.

Use of rescue medication

Use of rescue medication (number of puffs taken in the previous 12 h) was recorded morning and evening by the patient, in the electronic patient diary.

24-hour FEV_1 profile

In both pivotal studies a subset of patients performed 12 hour serial spirometry at Visit 3, at 6, 8, 10 and 12 hours post dose and twice a 24 hour serial spirometry at Visit 8/9 and Visit 12/13 and Visit 17/18 (A2303 only) at 16 and 22 hours post dose in addition. Together with the standard assessments where all patients were assessed in the clinic at 45 min and 15 min pre dose and 5, 15, 30 min, 1, 2, 3 and 4 hr post dose the 24-hour profile consisted of two individual pre dose measurements and a total of 13 individual FEV_1 measurements in 24 hours post dose.

Symptoms of COPD

At Visit 2 (Day −14) all patients were provided with an electronic patient diary to record morning and evening daily clinical symptoms; cough, wheezing, shortness of breath, sputum volume and colour, night time awakenings and rescue medication (salbutamol/albuterol) use.

The patients were instructed to routinely complete the diary twice daily, before taking study drug at the same time each morning and again (approximately 12 h later) each evening, considering events over the previous 12 h.

Other endpoints:

a) Inspiratory capacity

Inspiratory capacity measurements were performed first, before other spirometry measurements, and with approximately 3 minutes rest before proceeding with FEV_1 and FVC.

b) FVC

The forced vital capacity (FVC) was measured and registered together with the FEV_1 measurements.

Sample size

Both pivotal studies were designed with a very high probability to detect a clinical significant improvement in trough FEV_1 24 hours post dose of at least 120 ml. The standard deviation of the trough FEV_1 was estimated to be 270 ml.

A2303

The power to detect a difference of 120 mL in trough FEV_1 between NVA237 50 µg o.d. and placebo with standard deviation of 270 mL with 455 evaluable patients for NVA237 and 225 for placebo was more than 99% with a two-sided test at the 5 % significance level. From the assumption that 15% of patients would drop out without data for the primary endpoint at week 12, 535 patients for NVA237, 265 for placebo and 265 for tiotropium were to be randomised with a total sample size of 1065.

The minimal important clinical difference for TDI is 1 and from estimates that 28 % on placebo treatment and 42 % on NVA237 would improve at least 1 in TDI and assuming a drop out rate of 20% at week 26, 428 evaluable patients for NVA237 and 212 patients for placebo were to give a two-sided test at the 2.5% significance level with 89% power. Likewise for SGRQ, with a minimal important improvement of -4 and standard deviation of 13 and a drop out rate of 30% at week 52, 374 evaluable patients for NVA237 and 186 for placebo were to give a two-sided test at the 2.5% significance level with 88% power.

For superiority of tiotropium against placebo for trough FEV_1 after 12 weeks the power to detect a minimum difference of 120 mL with a two-sided test at the 5 % significance level with 225 evaluable patients for tiotropium and 225 patients on placebo was more than 99%.

A2304

The power to detect a difference of 120 mL in trough FEV_1 between NVA237 50 µg o.d. and placebo with standard deviation of 270 mL with 455 evaluable patients for NVA237 and 225 for placebo was more than 99% with a two-sided test at the 5 % significance level – identical to the power for A2303.

From the same assumptions on clinical relevance mentioned above for TDI and SGRQ and a drop out rate of 20% at week 26, a total sample size of 640 (428 NVA237 and 212 patients for placebo) provided the 2.5 % significance level (2 sided) with 88% power for TDI and 92% power for SGRQ.

Both pivotal phase III studies were well-powered to detect a clinically relevant improvement in lung function (trough FEV_1 post dose), relevant reduction in dyspnoea index and improvement in health related quality of life. Assuming that the estimated number of patients were included in all treatment arms, the likelihood of detecting significant improvements was 88 to more than 99%.

Randomisation

A2303

At Visit 3 (day 1), patients remained on allowed background COPD therapy consisting of inhaled corticosteroids (if appropriate) and short acting β2 agonists. They were randomized to double-blind treatment NVA237 50 µg o.d. or placebo, or to open-label tiotropium 18 µg in a ratio of 2:1:1.

Randomisation was stratified by:

1) smoking status (current or ex-smoker), (2) 12/24 hour serial spirometry subgroup (yes or no), and (3) Holter participant (yes or no). This resulted in 8 independently randomized pre-treatment strata. A treatment randomisation of 2:1:1 (NVA237: placebo: tiotropium) was maintained at the region, not center level.

A2304

At Visit 3, patients meeting the inclusion/exclusion criteria were randomized to receive double-blind NVA237 50 µg o.d. or placebo in a ratio of 2:1, for a 26 week treatment period.

Randomisation was stratified by:

1) smoking status (current or ex-smoker), (2) 12/24 hour serial spirometry subgroup (yes or no), and (3) Holter participant (yes or no) and/or PK (yes or no). This resulted in 8 independently randomized pre-treatment strata. A treatment randomisation of 2:1 (NVA237: placebo) was maintained at the region, not center level.

Blinding (masking)

In the comparisons of NVA237 and placebo in both pivotal studies patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomisation until database lock, using the following methods: (1) Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study; and (2) The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste and odour.

The third randomisation group in A2303 was treated with tiotropium in an open-label treatment arm as mentioned above.

Statistical methods

All efficacy variables were analyzed by treatment for the FAS or a subgroup of the FAS (e.g. the serial spirometry subgroups of the FAS). The PP population set was used for supportive analysis of the primary variable. All treatment contrasts with 95% confidence intervals (CIs) and p-values are presented. Significance after the multiplicity adjustment where appropriate were flagged. Multiplicity adjustment using the hierarchical procedure with Hochberg step up adjustment to control for type I error at 0.05 was applied for primary, key secondary and important secondary endpoints. For all other endpoints, the p-value was presented without flagging of significant results.

Results

Participant flow

A2303

A total of 1993 patients were screened and 1066 were randomized to treatment where a total of 810 patients (76.0 %) completed the study as planned. The most frequent reasons for screening failure were failing to meet the diagnostic/severity criteria and unacceptable test results (551 patients or 59%). The two most frequent reasons for discontinuing from treatment were withdrawal of consent and adverse events where study discontinuations occurred most frequently in the placebo group (Table 10-1).

Table 10-1 Patient disposition – n(%) of patients

Disposition Reason	NVA237 50 µg od. n (%)	Pbo n (%)	Tiotropium 18 µg od. n (%)	Total n (%)
Screened				1993
Randomized	529	269	268	1066
Completed	411 (77.7)	193 (71.7)	206 (76.9)	810 (76.0)
Discontinued	118 (22.3)	76 (28.3)	62 (23.1)	256 (24.0)
Primary reason for premature discontinuation				
Adverse Event(s)	40 (33.9)	29 (38.2)	18 (29.0)	87 (34.0)
Subject withdrew consent	40 (33.9)	23 (30.3)	26 (41.9)	89 (34.8)
Unsatisfactory therapeutic effect	20 (16.9)	9 (11.8)	6 (9.7)	35 (13.7)
Lost to follow-up	7 (5.9)	7 (9.2)	3 (4.8)	17 (6.6)
Protocol deviation	5 (4.2)	2 (2.6)	4 (6.5)	11 (4.3)
Administrative problems	4 (3.4)	1 (1.3)	2 (3.2)	7 (2.7)
Death	2 (1.7)	2 (2.6)	2 (3.2)	6 (2.3)
Abnormal laboratory value(s)	0	1 (1.3)	0	1 (0.4)
Abnormal test procedure result(s)	0	1 (1.3)	1 (1.6)	2 (0.8)
Patient's inability to use the device	0	1 (1.3)	0	1 (0.4)

Percentages of patients completed and discontinued are calculated with the number of randomized patients as the denominator.
Percentages of categories under "Primary reason for premature discontinuation" are calculated with the number of discontinued patients as the denominator.
Source: PT-Table 14.1-1.1

A2304

A total of 1324 patients were screened from 128 participating sites of which 822 were randomized to two treatment groups with 502 patients failing screening prior to randomisation. Of the 822 patients randomized to treatment, 662 (80.5%) completed the study as planned. The main reason for screening failure was failing to meet the protocol requirements of diagnostic/severity criteria and the two most common reasons for discontinuing from treatment was again withdrawal of consent and adverse events (Table 10-1).

Table 10-1 Patient disposition – n (%) of patients

Disposition Reason	NVA237 50 µg o.d. n (%)	Pbo n (%)	Total n (%)
Screened			1324
Randomized	552	270	822
Completed	450 (81.5)	212 (78.5)	662 (80.5)
Discontinued	102 (18.5)	58 (21.5)	160 (19.5)
Primary reason for premature discontinuation			
Subject withdrew consent	38 (37.3)	14 (24.1)	52 (32.5)
Adverse Event(s)	30 (29.4)	16 (27.6)	46 (28.8)
Administrative problems	21 (20.6)	13 (22.4)	34 (21.3)
Unsatisfactory therapeutic effect	5 (4.9)	5 (8.6)	10 (6.3)
Protocol deviation	4 (3.9)	3 (5.2)	7 (4.4)
Death	2 (2.0)	3 (5.2)	5 (3.1)
Lost to follow-up	1 (1.0)	2 (3.4)	3 (1.9)
Patient's inability to use the device	1 (1.0)	1 (1.7)	2 (1.3)
Subject's condition no longer requires study drug	0	1 (1.7)	1 (0.6)

Percentages of patients completed and discontinued are calculated with the number of randomized patients as the denominator.

Percentages of categories under "Primary reason from premature discontinuation" are calculated with the number of discontinued patients as the denominator.
Source: PT-Table 14.1-1.1

Recruitment

A2303: first patient had first visit on 29 June 2009 and last patient had the last visit on 28 April 2011.

A2304: first patient had first visit on 29 October 2009 and last patient had the last visit on 17 December 2010.

Conduct of the study

A2303

The study protocol was amended twice with the first amendment prior to study start where additional lung function measurements were included, further exacerbations in the study period tolerated, follow up period extended, the exclusion criteria were extended with exclusion of patients with other relevant chest diseases, supporting radiological evidence when pneumonia was suspected as AE and corrections of minor inconsistencies.

The second amendment took place after study termination but before study unblinding where the endpoint "days of poor control" was changed to "symptoms collected" because experience showed the end point was not well defined. For consistency reasons the term FAS (Full Analysis Set) replaced the term the ITT population.

Major protocol deviations, leading to exclusion from the per protocol population, occurred in 153 patients (14.4 %) and in a slightly higher percentage of patients in the placebo group than in patients randomized to NVA237 and tiotropium.

A2304

The protocol was only amended once before study start and involved incorporation of independent adjudication committee to assess the cause of death occurring during the study, replacement of the terms "safety population" or "ITT" with FAS (Full Analysis Set), addition of more baseline variables and addition of changes to "COPD exacerbations" definition where "the definition of 'COPD exacerbation' has been refined by adding 'moderate or severe' throughout the statistical sections."

Major protocol deviations, leading to exclusion from the per protocol population, occurred in 91 patients (11.1%) where the most frequent was non-compliance with time of dosing at the primary endpoint in 25 patients. It is stated that major deviations occurred in a higher percentage of patients in the placebo group (35 patients, 13.0%) as compared to patients treated with NVA237 (56 patients, 10.1 %)

Baseline data

In both studies basic demographics were comparable (Table 3) although a larger proportion of males was included in A2304 (81.9 %) than in A2303 (64.2%) perhaps because of more Asian (Japanese subgroup) patients in A2304 (35.4 %) than in A2303 (5.0%). There was also a difference in mean weight of the populations in the two studies where patients in A2303 had a mean weight of 79 kg in contrast to a mean of 72 kg in A2304. There was no difference in basic characteristics between treatment arms in either of the two studies.

Table 3: Demographics (safety population) for A2303 and A2304. Values are mean values for each variable.

Variable	**A2303** (n = 1060)	**A2304** (n = 817)
Age (years)	63.6	63.9
Gender – male (%)	64.2	81.9
Race – Asian (%)	5.0	35.4
Baseline height (cm)	168.9	166.9
Baseline weight (kg)	79.4	72.2

The disease characteristics as assessed at baseline was the same in the two studies

Table 4: Disease characteristics found for the safety population at baseline in the two pivotal studies on NVA237.

Variable	**A2303** (n = 1060)	**A2304** (n = 817)
Severity of COPD (GOLD 2008)		
- Moderate	678 (64.0 %)	497 (60.8 %)
- Severe	373 (35.2 %)	316 (38.7 %)
- Very severe	8 (0.8 %)	4 (0.5%)
Duration of COPD (years) mean	7.32	6.07
COPD exacerbation history		

- 0 - 1 - > 1	206 (76.9) 43 (16.0) 19 (7.1)	643 (78.7 %) 133 (16.3 %) 41 (5.0 %)
ICS use at baseline – yes (5)	568 (53.6)	437 (53.5 %)
Current smoker (%)	480 (45.3)	271 (33.,2 %)
Pack years	49.0	44.8

At visit 2, the screening examination included pre- and post-bronchodilator spirometry including reversibility to SAMA. Despite the inclusion criteria of moderate to severe COPD defined by a post bronchodilator FEV_1 > 30% predicted, 8 (A2303) and 4 (A2304) patients were actually included and randomised with an FEV_1 % predicted post bronchodilator value below 30% predicted. In both cases the deviation was marginal with a minimum value of post bronchodilator % predicted FEV_1 of 27.15 (A2303) and 28.21 (A2304).

Table 5: Key spirometry findings at visit 2, screening for the safety population in study A2303 and A2304. Each value is the mean value for the variable.

Variable	**A2303** (n = 1060)	**A2304** (n = 817)
FEV_1 (l) pre bronchodilator	1.357	1.320
FEV_1 (l) post bronchodilator	1.545	1.476
FEV_1 post bronchodilator (% predicted)	55.96	54.62
FEV_1 reversibility (%) post bronchodilator	15.85	13.67

Patients included in the two studies had the same baseline lung function with a mean FEV_1 % predicted post bronchodilator of 54.62 and 55.96 % respectively. The degree of reversibility was assessed with a SAMA (ipratropium bromide) and in both studies patients included showed a very high degree of reversibility with a mean increase in FEV_1 post bronchodilator of 15.85 and 13.67 % in A2303 and A2304. With a standard deviation of 14.9 and 14.1 respectively roughly 15 % of patients included in the two studies had a post bronchodilator reversibility of more than 30%. The maximum reversibility measured in one patient was 101 % and 89 % in A2303 and A2304.

Numbers analysed

As mentioned above, Study A2303 and A2304 employed the FAS (Full Analysis Set – all randomised patients who received at least one dose of study medication) as the ITT population in the protocol, while they defined the per protocol populations as patients who completed the studies without any predefined (defined prior to data lock and un blinding of data) major protocol deviations.

Table 6: The individual numbers analysed in study A2303 and A2304 in three different defined populations among participating patients.

Population	**A2303** (n = 1066)				**A2304** (n = 822)		
	Total	NVA237 (n = 529)	Placebo (n = 269)	Tiotropium (n = 268)	Total	NVA237 (n = 552)	Placebo (n = 270)
Randomized population	1066	529	269	268	822	552	270
Full Analysis Set	1060	525	268	267	794	534	260
Per Protocol population	904	451	223	230	703	478	225
FAS serial spirometry group	299	144	79	76	252	169	83

Approximately a third of the patient population in A2304 was Asian, which reflected the recruitment from India (147 patients), Korea (31 patients), Singapore (13 patients) and Japan (96 patients). Subgroup analysis was performed for the Japanese subgroup where, for example, 88 patients were analyzed for difference in trough FEV_1 at Day 1.

Outcomes and estimation

Efficacy results, primary objective

In both pivotal studies the through FEV_1 at week 12 was significantly higher in patients treated with NVA237 when compared to placebo. There was an absolute difference in the least square FEV_1 of 97 mL (A2303) and 108 mL (A2304) when compared to placebo for the full analysis set. In Study A2303, the increase in trough FEV_1 compared to placebo at week 12 was 83 mL for tiotropium.

Similarly for the PP population in A2303 both NVA237 and tiotropium were statistically significantly superior to placebo for trough FEV1 after 12 weeks of treatment with a treatment difference of 86 and 84 mL, respectively. Also in A2304 for the PP population NVA237 was statistically significantly superior to placebo for trough FEV1 after 12 weeks of treatment with a treatment difference of 111 mL.

Efficacy results, key secondary endpoints – TDI after 26 weeks

One of the key secondary endpoints in both pivotal studies was transitional dyspnoea index to indicate change in dyspnoea compared to baseline where the minimal important difference is an improvement of the score of 1 unit. In both studies a statistically significant decrease (positive score difference) in dyspnoea index was observed for the NVA237 group compared to placebo at week 26 where the difference in absolute score value was 0.81 (A2303) and 1.04 (A2304). For tiotropium the TDI after 26 weeks compared to placebo was increased in score to an absolute value of 0.94.

Efficacy results, key secondary effects – SGRQ after 26 weeks

The minimum important improvement is considered to be a lowering of the total score of 4 units. In both studies the treatment difference between NVA237 and placebo in SGRQ total score at week 26 in A2304 (- 2.81 units) and at week 52 in A2303 (- 3.32 units) was in favour of NVA237. In Study A2303, tiotropium was also significantly better than placebo, and similar results were demonstrated when NVA237 was compared with the active comparator.

Efficacy results, important secondary efficacy endpoints – COPD exacerbation

In both A2303 and A2304, time to first exacerbation was significantly increased with a hazard ratio compared to placebo of 0.66 and 0.69 respectively.

Among the additional secondary endpoints, Trough FEV_1 Day1, Week 26 and Week 52 (A2303 only) were all statistically significantly improved with NVA237 treatment compared to placebo (Tables 7 and 8 below).

Ancillary analyses

Subgroup analyses

The main subgroup analyses were performed as pooled analyses with population from both A2303 and A2304 where the effect of age, gender, smoking and other variables are analyzed. The results are presented below in the section on analysis performed across trials.

In A2304 a significant proportion of patients were Japanese and subgroup analysis was performed for this group on all significant efficacy variables. In short the results were as for the whole group of patients without any systematic difference. In some cases the efficacy results did not reach statistical significance where the reason was the lower number of patients in the Japanese subgroup. The superiority of NVA237 versus placebo in terms of trough FEV_1, the primary endpoint of this study, was consistent between the overall patient population and the Japanese subgroup, with a statistically significant treatment difference of 108 mL at Week 12.

Explorative efficacy results

In Study A2303 the inspiratory capacity (IC) was statistically significantly greater in the NVA237 and tiotropium groups than in the placebo group at nearly all assessed time points at Day 1, Week 12, Week 26 and Week 52 where the only exceptions were in pre-dose measurements.

This result was confirmed in Study A2304 where IC was statistically significantly greater in the NVA237 group than in the placebo group at all assessed time points. The treatment difference at Week 26 at trough (23 h 40 min) was 113 mL ($p<0.001$).

As a measure of medical resource utilisation, the number of hospital admissions, emergency room visits and unscheduled doctor's visits during the 26 (A2304) or 52 (A2303) week long observational period was registered.

In both pivotal studies, the frequency of the three measures of medical resource utilisation was very low in both active treatment arms and placebo arms. In Study A2304, the majority of patients had no hospital admissions (98.2% in the NVA237 group and 95.9% in the placebo group). A total of 2.6% of patients overall had ≥ 1 hospital admission. More patients in the placebo group (4.1%) than in the NVA237 group (1.8%) had at least one hospital admission. In Study A2303, 96.6 % in the NVA237 group, 94.8 % in the tiotropium group and 94.0 % in the placebo group had no hospital admissions during the 52 week treatment period.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7. Summary of Efficacy for trial A2303

Title: 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			
Study identifier	CNVA237A2303, EudraCT no. 2008-008394-63		
Design	A 52-week treatment, randomized, double-blind, placebo-controlled, with open label tiotropium, parallel-group study		
	Duration of main phase:	52 weeks	
	Duration of Run-in phase:	14 days	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority		
Treatments groups	NVA237A 50 µg		NVA237A 50 µg od., 52 weeks, 529 randomized
	Placebo		placebo, 52 weeks, 269 randomized
	Tiotropium 18 µg o.d.		Tiotropium 18 µg o.d., 52 weeks, 268 randomized
Endpoints and definitions	Primary	Trough FEV1	Mean of FEV1 at 23 h 15 min and 23 h 45 min post dose, after 12 weeks of treatment.
	Secondary	TDI	TDI focal score at week 26
	Secondary	SGRQ	SGRQ total score at week 52
	Secondary	Time to first moderate / severe COPD exacerbation	Time to first moderate / severe COPD exacerbation over 52 weeks
	Secondary	Rescue medication usage	Daily rescue medication use over 52 weeks (number of puffs)
Database lock	20-Jun-2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo	Tiotropium 18 µg o.d.
	Number of subjects	513	245	253
	Trough FEV1 at week 12, LS mean (L)	1.469	1.372	1.455
	SE	0.0141	0.0173	0.0170
Effect estimate per comparison	Trough FEV1 at Week 12	Comparison groups	NVA - Placebo	

		LS mean (L)	0.097
		SE	0.0167
		P-value	<0.001
	Trough FEV1 at Week 12	Comparison groups	Tio - Placebo
		LS mean (L)	0.083
		SE	0.0193
		P-value	<0.001

Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo	Tiotropium 18 µg o.d.
	Number of subjects	470	217	238
	TDI focal score at Week 26	2.13	1.32	2.26
	SE	0.240	0.289	0.281

Effect estimate per comparison	TDI focal score at Week 26	Comparison groups	NVA - Placebo
		LS mean	0.81
		SE	0.260
		P-value	0.002
	TDI focal score at Week 26	Comparison groups	Tio - Placebo
		LS mean	0.94
		SE	0.297
		P-value	0.002

Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo	Tiotropium 18 µg o.d.
	Number of subjects	499	248	251
	SGRQ Total Score at Week 52	40.85	44.16	41.32
	SE	0.854	1.040	1.024

Effect estimate per comparison	SGRQ Total Score at Week 52	Comparison groups	NVA - Placebo
		LS mean	-3.32
		SE	1.004
		P-value	<0.001
	SGRQ Total Score at Week 52	Comparison groups	Tio - Placebo
		LS mean	-2.84
		SE	1.155
		P-value	0.014

Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo	Tiotropium 18 µg o.d.
	Number of subjects	524	266	266
	Number of patients with >=1 moderate / severe COPD exacerbation	172	107	80

Effect estimate per comparison	Time to first moderate or severe COPD exacerbation	Comparison groups	NVA - Placebo
		Hazard Ratio	0.66
		P-value	0.001
	Time to first moderate or severe COPD exacerbation	Comparison groups	Tio - Placebo
		Hazard Ratio	0.61
		P-value	0.001

Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo	Tiotropium 18 µg o.d.
	Number of subjects	523	263	263
	Change from baseline in mean daily number of puffs of rescue medication	-1.58	-1.20	-1.83
	SE	0.151	0.184	0.183

Effect estimate per comparison	Change from baseline in mean daily number of puffs of rescue medication	Comparison groups	NVA - Placebo
		LS mean	-0.37
		SE	0.181
		P-value	0.039
	Change from baseline in mean daily number of puffs of rescue medication	Comparison groups	Tio - Placebo
		LS mean	-0.63
		SE	0.209
		P-value	0.003

Analysis description	The FEV1, TDI. SGRQ and rescue medication use were analysed using a mixed model for the FAS with baseline value, baseline ICS use (Yes/No), FEV1 prior to inhalation of short acting bronchodilator and FEV_1 45 min post inhalation of short acting bronchodilator as covariates and treatment, smoking status (current/ex-smoker) and region as fixed effects with center nested within region as a random effect. Analysis of time to first moderate or severe COPD exacerbation used Cox regression model, including terms for treatment, baseline inhaled corticosteroid use (Yes/No), baseline total symptom score, COPD exacerbation history (the number of moderate or severe COPD exacerbations in the year prior to screening), FEV_1 prior to inhalation of short acting bronchodilator, FEV_1 45 min post inhalation of short acting bronchodilator, smoking history, region.

Table 8. Summary of Efficacy for trial A2304

Title: 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			
Study identifier	CNVA237A2304, EudraCT no. 2009-013504-32		
Design	A 26-week treatment, randomized, double-blind, placebo-controlled, parallel-group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks 14 days not applicable
Hypothesis	Superiority		
Treatments groups	NVA237A 50 µg		NVA237A 50 µg od., 26 weeks, 552 randomized
	Placebo		placebo, 26 weeks, 270 randomized
Endpoints and definitions	Primary	Trough FEV1	(at 23 h 15 min and 23 h 45 min post dose) after 12 weeks of treatment.
	Secondary	TDI	TDI focal score at week 26
	Secondary	SGRQ	SGRQ total score at week 26
	Secondary	Time to first moderate / severe COPD exacerbation	Time to first moderate / severe COPD exacerbation over 26 weeks
	Secondary	Rescue medication usage	Daily rescue medication use over 26 weeks (number of puffs)
Database lock	24-Jan-2011		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol		
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo
	Number of subject	512	243
	Trough FEV1 at week 12 *(least squares mean)(L)*	1.408	1.301
	SE	0.0105	0.0137
Effect estimate per comparison	Trough FEV1 at Week 12	Comparison groups	NVA - Placebo
		LS mean (L)	0.108
		SE	0.0148
		P-value	<0.001
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo
	Number of subjects	493	240
	TDI focal score at Week 26	1.84	0.80
	SE	0.257	0.294
Effect estimate per comparison	TDI focal score at Week 26	Comparison groups	NVA - Placebo
		LS mean	1.04
		SE	0.235
		P-value	<0.001
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo
	Number of subjects	502	246
	SGRQ Total Score at Week 26	39.50	42.31
	SE	0.813	0.992
Effect estimate per comparison	SGRQ Total Score at Week 26	Comparison groups	NVA - Placebo
		LS mean	−2.81
		SE	0.961
		P-value	0.004
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo
	Number of subjects	532	260

	Number of patients with >=1 moderate / severe COPD exacerbation	93	63
Effect estimate per comparison	Time to first moderate or severe COPD exacerbation	Comparison groups	NVA - Placebo
		Hazard Ratio	0.69
		P-value	0.023
Descriptive statistics and estimate variability	Treatment group	NVA237A 50 µg	Placebo
	Number of subjects	529	259
	Change from baseline in mean daily number of puffs of rescue medication	-1.21	-0.75
	SE	0.122	0.156
Effect estimate per comparison	Change from baseline in mean daily number of puffs of rescue medication	Comparison groups	NVA - Placebo
		LS mean	-0.46
		SE	0.164
		P-value	0.005
Analysis description	The FEV1, TDI. SGRQ and rescue medication use were analysed using a mixed model for the FAS with baseline value, baseline ICS use (Yes/No), FEV_1 prior to inhalation of short acting bronchodilator and FEV_1 45 min post inhalation of short acting bronchodilator as covariates and treatment, smoking status (current/ex-smoker) and region as fixed effects with center nested within region as a random effect. Analysis of time to first moderate or severe COPD exacerbation used Cox regression model, including terms for treatment, baseline inhaled corticosteroid use (Yes/No), baseline total symptom score, COPD exacerbation history (the number of moderate or severe COPD exacerbations in the year prior to screening), FEV_1 prior to inhalation of short acting bronchodilator, FEV_1 45 min post inhalation of short acting bronchodilator, smoking history, region.		

Analysis performed across trials (pooled analyses and meta-analysis)

The Applicant has conducted an extensive pooled analysis of the two pivotal studies, A2303 and A2304. The two pivotal studies individually demonstrate statistically significant effects in all key variables when NVA237 were compared to placebo treatment. As such the supportive evidence from pooled analyses of efficacy data becomes less important in the efficacy analysis of NVA237 compared to placebo. The most important analyses performed across the two pivotal studies are subgroup analyses on basic patients profile data to detect possible differences in treatment effects observed in different patient groups.

The pooled population included 1,888 randomized patients, of which 78.0% completed the studies. The pooled population included 1,888 randomized patients, of which 78.0% completed the studies. Approximately half the patients in each group were using ICS at baseline, 59.6% of the patients were ex-smokers, and the overall mean smoking history was 47.6 pack years. The mean post-bronchodilator % predicted FEV_1 was 55.5%. Mean reversibility to ipratropium bromide (80 µg) was 15.1%.

In terms of efficacy results overall the pooled analysis reflected and supported the individual replicated results seen in the two pivotal studies. For the primary endpoint trough FEV_1 at week 12 the individual studies showed an increase in comparison to placebo in through FEV_1 of 108 and 97 mL in A2304 and A2303 respectively with 95% confidence intervals of 79 to 137 mL and 65 to 130 mL in the two studies with populations of NVA237 treated patients of 512 and 513 patients. In the pooled analysis where 1059 patients treated with NCV237 50 µg once daily was compared to 528 patients treated with placebo the mean difference in through FEV_1 Week 12 was 103 mL and with a narrower 95% confidence interval of between 81 mL and 125 mL.

Clinical studies in special populations

The applicant has conducted a study in renal impairment which showed an increase in exposure (AUClast) of up to 1.4-fold in subjects with mild and moderate impairment, as compared to healthy controls. An increase of up to 2.2-fold was seen in subjects with severe renal impairment.

No study in hepatic impairment was conducted on the basis that renal elimination is predominant.

There is no specific study in the elderly. Population PK modelling suggested an increase in exposure with increasing age of about 70% between patients in their 40s and those of 80+.

Supportive studies

A2310

The study was a multi-centre, double-blind, randomized, placebo-controlled, two-period cross-over study. There were two 3-week treatment periods with each treatment period being separated by a 14–day wash-out (wash-out period could be expanded up to 28 days, if required for logistical reasons) (Figure 9-1). A planned number of approximately 80 patients with moderate to severe COPD were to be randomized to receive one of two treatment sequences:

NVA237 followed by matched placebo or placebo followed by NVA237.

The primary objective was to determine the effect of 50 µg NVA237 compared with matching placebo inhaled once daily on exercise tolerance as measured by exercise endurance time during a sub-maximal constant-load cycle ergometry test (SMETT) after three weeks of treatment.

The sub-maximal constant-load cycle ergometry (Baseline, Day 1, Day 21 of both treatment periods) was defined as an exercise procedure where the patient cycles at 80% of the Wmax value achieved at a previous incremental exercise test.

A total of 108 patients were randomized to the study, where 99 patients contributed to the pharmacodynamic profile of NVA 237 (PD analysis set).

NVA237 treatment was statistically significantly superior to placebo with respect to patients exercise endurance time after 3 weeks (at Day 21) of treatment. The LS mean treatment difference was 88.93 sec with a p-value <0.001; an improvement by NVA237 of about 21%.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development of NVA237 consisted of a total of 12 studies: five Phase I studies (NVA237A2103, A2104, A2105, A2108, and A2109), four Phase II studies (NVA237A2205, A2206, A2207 and A2208) and three Phase III studies (NVA237A2304, A2303 and A2310).

The NVA237 program was based, amongst others, on the EMA's *"Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with Chronic Obstructive Pulmonary Disease (COPD)"*.

With respect to the overall efficacy documentation, the Applicant has chosen a very detailed and comprehensive programme of both objective endpoints and measures of symptomatic improvement in both pivotal studies.

In all 6 phase II and phase III studies not the most robust clinical criteria have been used to exclude patients suspected of asthma disease. However, despite the fact that the exclusion of asthma is mainly based on medical records and history, the inclusion and exclusion criteria employed in the pivotal clinical studies are considered sufficient to ensure that enrolled patient reflect a general population of patients with moderate-severe COPD. It should be noted that the degree of reversibility of airflow limitation as measured by FEV_1 before and after bronchodilator is no longer recommended to aid the differential diagnosis with asthma (GOLD 2011).

On dose finding, specific dose response studies with double blind, randomised, placebo controlled design are required. In the present application, the decisive dose finding study is Study A2205 where NVA237 50 µg once daily results in a mean increase in through FEV_1 over placebo of 131 mL where NVA237 25 µg only increased through FEV_1 90 mL over placebo and NVA237 100 µg was comparable to 50 µg with an increase in through FEV_1 of 142 mL over placebo with a minimum clinical important difference in through FEV_1 of 100-140 mL. This result was confirmed in A2208. Both studies were double blind, placebo controlled studies.

As to the dosing frequency, Study A2208 in a large and complicated design shows that trough FEV_1 is increased with 109 mL on NVA237 50 µg once daily and increased with 141 mL on NVA237 25 FEV_1 twice daily. Further analyses have been provided indicating that the difference between NVA237 and placebo AUC FEV_1 is maintained over 24 hours with 50 µg once daily, but that there is drop-off from 12 to 24 hours.

The efficacy of the selected once daily regimen has been clearly demonstrated and offers a benefit regarding patient compliance. However, some limited data suggest that inhaling 25 µg twice daily instead of 50 µg once daily may possibly be a better dose schedule in terms of safety and efficacy. In order to address this, the CHMP requested a post-authorisation clinical study to further characterise the optimal dosing schedule for NVA237. "Optimal dosing schedule" was considered as important missing information at the time of Opinion and should be added in the RMP. The study will be a 26-week treatment, multi-center, randomized, double-blind, parallel-group study to compare the efficacy, safety and tolerability of NVA237 given once and twice daily in patients with stable Chronic Obstructive Pulmonary Disease and moderate to severe airflow obstruction.

Efficacy data and additional analyses

The outcomes of both studies are consistent and show clinically relevant improvements in most outcome measures. In both studies an increase in primary endpoint trough FEV_1 week 12 statistically significant superior to placebo and above or at the minimum clinical important difference is documented, and the improvement in lung function is supported by different means of lung function

and by numerous repeated measurements over time (24 h) and 26 to 52 weeks, where all measurements show consistent improvements over placebo. Symptomatic benefit is also documented in both studies from improvements in TDI and SGRQ over time when NVA237 50 µg once daily is compared to placebo. But it should be noted that the effects on these symptomatic measures are not very large as the clinically significant differences expected to be found are either not met in SGQR in any of the pivotal studies or not met in TDI (Study A2303) or borderline achieved (Study A2304). Both studies also document a modest, but relevant decrease in frequency of moderate and severe COPD exacerbations and improvement in terms of use of rescue medication in NVA 237-treated patients compared to placebo. However, the totality of the efficacy data from the pivotal studies (spirometry, exacerbations and patient-reported outcomes, use of rescue medication etc.) are considered to reflect a clinically relevant benefit in COPD patients.

Clinical efficacy of NVA237 is supported by the open label comparison with the long acting muscarinic antagonist tiotropium where efficacy measures generally show similar or numerically better results of NVA237 compared to tiotropium.

In the third supportive phase III clinical trial (Study A2310), efficacy is further documented by a statistically significant increase in exercise endurance in seconds in patients treated with NVA237 and compared to placebo where exercise endurance increases 21% over placebo.

Subgroup analysis was performed in the pooled populations of studies A2303 and A2304 where there were no systematic efficacy differences in relation to relevant demographic factors (age, gender, race and region) and no systematic efficacy differences in relation to smoking status, use of ICS or COPD severity. Objective lung function outcomes appear to correlate with baseline reversibility: i.e. patients with greater reversibility having a better lung function benefit. This is not an unexpected finding considering the pharmacological mechanism of the drug. The relation between baseline reversibility and symptomatic outcomes is not as strong. There are statistically significant benefits of NVA 237 over placebo in terms of trough FEV_1 for all the tested reversibility groups, but the clinical relevance is questionable in the low reversibility groups. However, it is considered that these subgroup analyses do not justify requiring reversibility testing and restricting NVA 237 therapy to patients exhibiting a high degree of reversibility at treatment start.

2.5.4. Conclusions on the clinical efficacy

In conclusion, the efficacy of NVA237 50 µg once daily over placebo in terms of improvement in lung function measurements and relevant measures of symptomatic benefit has been documented in the two pivotal studies and is supported by a phase II study and a further phase III study.

According to Study A2208, the NVA237 25 µg twice daily regimen offers a benefit in trough FEV_1 over NVA237 50 µg once daily. However, this data is limited, the efficacy of the once daily regimen has been clearly demonstrated and it offers a benefit regarding patient compliance. In order to address this, the CHMP considers the following measure necessary:

The applicant will conduct a post-authorisation clinical study to further characterise the optimal dosing schedule for NVA237. "Optimal dosing schedule" was considered as important missing information at the time of Opinion and should be added in the RMP. The study will be a 26-week treatment, multi-center, randomized, double-blind, parallel-group study to compare the efficacy, safety and tolerability of NVA237 given once and twice daily in patients with stable Chronic Obstructive Pulmonary Disease and moderate to severe airflow obstruction).

2.6. Clinical safety

Patient exposure

At the data lock point for the Summary of Clinical Safety provided by the Applicant, 2296 patients had been treated with NVA237 (including all inhaled dosages and dose regimens), for a total of about 773 patient-years. The Major Safety database includes 2436 patients, 1353 of whom received NVA237 treatment; exposure in total patient-years for patients who received NVA237 was about 712 patient-years. The Short-term Safety database includes 1242 COPD patients receiving doses of NVA237 ranging from 12.5 µg to 200 µg. The overall mean exposure for patients who received short-term treatment in the NVA237 50 µg group was 0.3 patient-years.

A summary of the number of patients exposed and the duration of exposure for the Core 6-month Safety database and the Core 12-month Safety database is presented in Table 1-6 and Table 1-7, respectively.

Table 1-6 Duration of exposure to study drug after randomization - COPD Core 6-month Safety database

Duration of exposure		NVA237 50 µg o.d. N=1075	Tiotropium 18 µg o.d. N=267	Placebo N=535
Exposure (days)				
	Mean (SD)	163.7 (46.96)	166.0 (44.76)	157.5 (55.54)
	Min	1	1	1
	Median	182.0	182.0	182.0
	Max	203	182	221
Categorized exposure				
Overall	n (%) of patients	1075 (100.00)	267 (100.00)	535 (100.00)
	Total patient-years	481.71	121.32	230.69
≥ 12 weeks	n (%) of patients	965 (89.77)	244 (91.39)	458 (85.61)
≥ 26 weeks*	n (%) of patients	842 (78.33)	229 (85.77)	399 (74.58)

Duration of exposure = date of last dose - date of first dose + 1.

* Some patients in Study A2304 had slightly longer exposure than 26 weeks.

Table 1-7 Duration of exposure to study drug after randomization - COPD Core 12-month Safety database

Duration of exposure		NVA237 50 µg o.d. N=525	Tiotropium 18 µg o.d. N=267	Placebo N=268
Exposure (days)				
	Mean (SD)	314.8 (107.97)	315.8 (107.42)	295.6 (126.04)
	Min	2	1	1
	Median	365.0	365.0	365.0
	Max	401	393	413
Categorized exposure				
Overall	n (%) of patients	525 (100.00)	267 (100.00)	268 (100.00)
	Total patient-years	452.43	230.83	216.90
≥ 12 weeks	n (%) of patients	480 (91.43)	244 (91.39)	231 (86.19)
≥ 26 weeks	n (%) of patients	444 (84.57)	229 (85.77)	214 (79.85)
≥ 38 weeks	n (%) of patients	428 (81.52)	218 (81.65)	204 (76.12)

Duration of exposure = date of last dose - date of first dose + 1.

The 6-month and 12-month exposure to NVA237 at the applied dose (50 µg group) comfortably exceed the recommended numbers in the guideline (300-600 and 100 patients, respectively).

The number of COPD patients exposed to NVA237 at 50 µg o.d. irrespective of exposure duration is n=1361.

Adverse events

Summaries of AEs and SAEs are based on treatment-emergent (i.e. newly occurring or worsening) undesirable signs, symptoms, or medical conditions after the first dose of study drug, including events likely to be related to the underlying disease or likely to represent concomitant illness. Any AEs whose start dates were before the first dose date were considered as medical history. The reporting of AEs covers common AEs, SAEs/death, and other significant AEs. The occurrence of AEs was detected by non-directive questioning of the patient at each visit during the study, when they were volunteered by the patient during or between visits, or through physical examination, laboratory test, or other assessments. Patients also recorded daily clinical symptoms in an electronic diary.

AEs are summarized by preferred term for the most frequent AEs (≥ 1.5% in any group) in the Core 6-month Safety database in Table 2-1 (below). The 1.5% threshold used in the summary table was chosen to enable concise presentation based on overall AE frequencies.

Table 2-1 Adverse events by preferred term (at least 1.5% in any group) (COPD Core 6-month Safety database)

MedDRA preferred term	NVA237 50 µg o.d. N=1075 n (%)	Tiotropium 18 µg o.d. N=267 n (%)	Placebo N=535 n (%)
Any preferred term	643 (59.81)	174 (65.17)	357 (66.73)
Chronic obstructive pulmonary disease	241 (22.42)	74 (27.72)	162 (30.28)
Upper respiratory tract infection	64 (5.95)	19 (7.12)	43 (8.04)
Nasopharyngitis	57 (5.30)	16 (5.99)	31 (5.79)
Cough	40 (3.72)	11 (4.12)	24 (4.49)
Upper respiratory tract infection bacterial	38 (3.53)	14 (5.24)	31 (5.79)
Headache	35 (3.26)	7 (2.62)	20 (3.74)
Back pain	32 (2.98)	8 (3.00)	15 (2.80)
Dyspnoea	29 (2.70)	3 (1.12)	23 (4.30)
Dry mouth	24 (2.23)	4 (1.50)	6 (1.12)
Sinusitis	24 (2.23)	5 (1.87)	13 (2.43)
Hypertension	23 (2.14)	11 (4.12)	13 (2.43)
Lower respiratory tract infection	23 (2.14)	9 (3.37)	14 (2.62)
Pyrexia	20 (1.86)	1 (0.37)	15 (2.80)
Bronchitis	19 (1.77)	9 (3.37)	11 (2.06)
Urinary tract infection	19 (1.77)	10 (3.75)	10 (1.87)
Diarrhoea	16 (1.49)	4 (1.50)	7 (1.31)
Insomnia	11 (1.02)	4 (1.50)	4 (0.35)
Pneumonia	11 (1.02)	5 (1.87)	11 (2.06)
Viral upper respiratory tract infection	11 (1.02)	8 (3.00)	15 (2.80)
Arthralgia	10 (0.93)	4 (1.50)	9 (1.68)
Constipation	10 (0.93)	0	8 (1.50)
Dizziness	9 (0.84)	5 (1.87)	7 (1.31)
Oedema peripheral	9 (0.84)	5 (1.87)	7 (1.31)
Nasal congestion	8 (0.74)	4 (1.50)	5 (0.93)
Nausea	7 (0.65)	2 (0.75)	8 (1.50)
Non-cardiac chest pain	7 (0.65)	6 (2.25)	4 (0.75)
Pharyngitis	7 (0.65)	4 (1.50)	3 (0.56)
Dysphonia	5 (0.47)	4 (1.50)	3 (0.56)
Rhinorrhoea	4 (0.37)	2 (0.75)	10 (1.87)

The data are based on 2 different sources, AE eCRF and COPD exacerbation episode eCRF.
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple AEs is counted only once in the any preferred term row.
Only AEs reported while on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.
Preferred terms are sorted in descending order of frequency in the NVA237 50 µg o.d. group.

The overall frequency of AEs in the Core 6-month Safety database was lower in the NVA237 group (59.8%) compared to the placebo (66.7%) and tiotropium treatment groups (65.2%). The most frequent AE by preferred term was COPD, which was reported less frequently in the NVA237 and tiotropium groups compared with the placebo group. Other frequent AEs were upper respiratory tract

infection (URTI), nasopharyngitis, cough, bacterial URTI, and headache. All of these events were reported with lower frequency in the NVA237 group as compared to the placebo group.

Typical anticholinergic AEs that were more frequent in the NVA237 group than the placebo and tiotropium groups in the Core 6-month Safety database included dry mouth (2.2% for the NVA237 group, 1.1% in the placebo group, and 1.5% in the tiotropium group), as AEs were less frequent in the NVA237 and tiotropium groups compared to the placebo group for constipation (NVA237 0.9%, placebo 1.5%, and tiotropium 0) and blurred vision (NVA237 0.5%, placebo 0.6%, and tiotropium 0.4%). Benign prostatic hyperplasia was reported in the NVA237 and tiotropium groups (0.3% and 0.8%, respectively), but not in the placebo group. Glaucoma was reported in 1 patient (0.1%) in the NVA237 group but not in the placebo or tiotropium groups (not apparent from table). Urinary tract infection was more frequent in the tiotropium group (3.8%) than the NVA237 and placebo groups (1.8% and 1.9%, respectively) (Table 2-1). Overall, the frequency of these events was low.

In the Core 6-month Safety database, AEs with an absolute frequency in the NVA237 group of at least 0.5% (corresponding to approximately 5 patients) and at least a 1.5-fold higher frequency than in the placebo group were defined as potential ADRs and tabulated below:

Table 2-5 Potential adverse drug reactions based on numerical criteria (COPD Core 6-month Safety database)

Preferred Term	NVA237 50 µg o.d. N=1075	Placebo N=535	OR (95% CI) NVA237 50 µg o.d. vs Placebo
Dry mouth	24 (2.23)	6 (1.12)	2.034 (0.826, 5.011)
Pain in extremity	10 (0.93)	1 (0.19)	5.029 (0.642, 39.387)
Rash	10 (0.93)	2 (0.37)	2.503 (0.547,11.465)
Asthenia	8 (0.74)	2 (0.37)	n.e.
Dyspepsia	8 (0.74)	2 (0.37)	2.009 (0.425, 9.498)
Gastroenteritis viral	8 (0.74)	2 (0.37)	2.020 (0.427, 9.554)
Hyperglycaemia	8 (0.74)	2 (0.37)	n.e.
Rhinitis	8 (0.74)	2 (0.37)	2.020 (0.427, 9.554)
Sinus congestion	8 (0.74)	2 (0.37)	2.020 (0.427, 9.552)
Dysuria	7 (0.65)	1 (0.19)	3.481 (0.427, 28.367)
Productive cough	7 (0.65)	1 (0.19)	3.525 (0.432, 28.733)
Atrial fibrillation	6 (0.56)	0	n.e.
Hypercholesterolaemia	6 (0.56)	1 (0.19)	n.e.
Throat irritation	6 (0.56)	1 (0.19)	3.033 (0.364, 25.276)

n.e.= not evaluable from the logisitic regresssion model due to 0 events in the tiotropium arm

To reach statisitical significance, the lower bound of the 95% confidence interval must be greater than 1.

Despite the fact that none of the OR confidence intervals for potential adverse drug reaction frequencies NVA237 vs. placebo excluded 1, it appears evident that dry mouth is truly an adverse drug reaction related to NVA237 taking the pharmacological mode of action into consideration.

Dysuria is reported in notably more patients on NVA237 than in the placebo group. Although not very typical, this could possibly represent an anticholinergic effect of NVA237. Also other anticholinergic adverse events appear to be more frequent in the NVA237 (and the tiotropium) group than in the placebo group, although in small numbers and not apparent from the table above.

Atrial fibrillation when reported as adverse events occurred more frequently among NVA237-treated patients (and in patients on tiotropium) than in patients on placebo. But when looking at adjudicated ECG recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was

similar for NVA237 and placebo. However, atrial fibrillation has been inserted in section 4.8 of the SmPC and included in the RMP as a potential risk.

For the remaining adverse events where an excess in NVA237-treated patients was shown, the differences could very well be chance findings.

Serious adverse event/deaths/other significant events

In all completed studies, a total of 14 deaths occurred, which included 12 patients who died during the active treatment period and 2 patients who died during the 30 day follow-up period. Seven of these deaths occurred in the NVA237 group, 5 deaths occurred in the placebo group, and 2 deaths occurred in the tiotropium group.

There is no indication that any of the death cases were causally related to treatment with NVA237.

The table summarizes SAEs by primary system organ class and preferred term (occurring in at least 2 patients in any treatment group) in the Core 6-month Safety database.

Table 2-15 **Serious adverse events by system organ class and preferrred term (>= 2 patients with an event in any treatment group) – (COPD Core 6-month Safety database)**

Primary MedDRA system organ class MedDRA preferred term	NVA237 50 µg o.d. N=1075 n (%)	Tiotropium 18 µg o.d. N=267 n (%)	Placebo N=535 n (%)
Any primary system organ class	75 (6.98)	25 (9.36)	53 (9.91)
Cardiac disorders	12 (1.12)	2 (0.75)	10 (1.87)
Atrial fibrillation	4 (0.37)	0	0
Acute coronary syndrome	2 (0.19)	0	0
Cardiac failure congestive	2 (0.19)	0	1 (0.19)
Myocardial infarction	2 (0.19)	1 (0.37)	1 (0.19)
Angina pectoris	0	0	2 (0.37)
Myocardial ischaemia	0	0	2 (0.37)
Gastrointestinal disorders	4 (0.37)	2 (0.75)	6 (1.12)
Vomiting	0	0	2 (0.37)
General disorders and administration site conditions	2 (0.19)	2 (0.75)	3 (0.56)
Non-cardiac chest pain	1 (0.09)	2 (0.75)	0
Pyrexia	0	0	2 (0.37)
Infections and infestations	15 (1.40)	9 (3.37)	17 (3.18)
Pneumonia	6 (0.56)	4 (1.50)	7 (1.31)
Upper respiratory tract infection bacterial	3 (0.28)	1 (0.37)	5 (0.93)
Bronchitis	2 (0.19)	0	1 (0.19)
Lower respiratory tract infection	2 (0.19)	0	1 (0.19)
Upper respiratory tract infection	0	1 (0.37)	2 (0.37)
Injury, poisoning and procedural complications	8 (0.74)	4 (1.50)	2 (0.37)
Metabolism and nutrition disorders	5 (0.47)	0	3 (0.56)
Dehydration	4 (0.37)	0	3 (0.56)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (1.02)	1 (0.37)	7 (1.31)
Lung neoplasm	2 (0.19)	0	0
Nervous system disorders	7 (0.65)	1 (0.37)	3 (0.56)
Syncope	3 (0.28)	0	0
Transient ischaemic attack	2 (0.19)	0	1 (0.19)
Respiratory, thoracic and mediastinal disorders	25 (2.33)	9 (3.37)	24 (4.49)
Chronic obstructive pulmonary disease	18 (1.67)	6 (2.25)	23 (4.30)
Respiratory failure	3 (0.28)	1 (0.37)	3 (0.56)
Acute respiratory failure	2 (0.19)	0	0
Dyspnoea	2 (0.19)	0	2 (0.37)

Overall the frequency and nature of serious adverse events are considered to be typical for a moderate to severe COPD population. Acute coronary syndrome/myocardial infarction were reported in slightly more patients treated with NVA237 compared to patients treated with placebo or tiotropium. However, when taking number of patients in the treatment groups as well as exposure into account, there is no suggestion of any significant excess on NVA237.

Laboratory findings

Laboratory data submitted by the Applicant included haematology, blood chemistry, and urinalysis. The reporting was presented only for the COPD Major Safety database using the International System (SI) units.

Overall, the haematology results are unremarkable. There was a slight imbalance with regard to clinically notable decrease in haemoglobin in the NVA237 group compared to the placebo and tiotropium groups, but this could very well be a chance finding and was not considered to be clinically significant.

The clinical chemistry and urinalysis results are overall considered to be unremarkable.

Systolic and diastolic pressure results were not suggestive of any relevant difference between treatment groups.

Notably low pulse rates were more common in the NVA237 group (and the tiotropium group) at all time intervals than in the placebo group. This is not readily explained by the pharmacology of the NVA237. It may be an effect of NVA 237 (a bradycardic effect was seen with a larger inhaled dose in the thorough QTc study), but it could also be caused by the fact that patients in the placebo group were more frequently treated with beta2-agonists. The finding was not considered clinically significant.

Notably higher body weight was more frequent in the NVA237 group compared to the placebo group after 6 months and after 12 months. Although numerical differences were small, body weight mean difference from baseline was larger for NVA235-treated patients than for patients on placebo. The finding could be secondary to the efficacy advantage associated with NVA 237 (COPD patients are often underweight). It was not considered to be clinically significant.

With regard to ECG, for most time points, the mean change from baseline in QTcF was larger in NVA237-treated patients than in placebo-treated patients. However, the differences were very small (up to 1.9 ms), and the pattern was not consistent. There are no consistent, relevant differences between NVA237 and placebo in the categorical analyses of patients experiencing high QTcF values or patients experiencing large increases in QTcF.

Safety in special populations

AEs were evaluated in demographic subgroups (age, gender, and race), by baseline characteristics (COPD severity, and CCV risk factors) by exposure category and baseline steroid use.

Effect of age

Overall and for respiratory, thoracic and mediastinal disorders (1st most frequent SOC) and for musculoskeletal and connective tissue disorders (3rd most frequent SOC), there was no clear tendency that elderly patients experienced adverse events more frequently than younger patients. When adjusting for the frequencies in the placebo group, there was no clear indication that NVA237 caused a higher adverse event reporting in elderly patients compared to younger patients. However, the number of patients in the 75+ years group was low.

Of all AEs reported on NVA237 in the >75 years group, 91% had a placebo-corrected difference in the AE frequency of less than one per cent compared to the younger age groups. The frequency was > 1% higher for 13/138 AEs and 12/203 AEs in the group of >75 years than in that of 65-75 years and <65 years respectively. Of these headache and urinary tract infection were reported most frequently in the >75 years population and is proposed to be mentioned in the SmPC.

Table 10-1 Number of patients (percent) of adverse events on NVA237 by age groups in the Major COPD safety database

	Number (percent) of patients			
	<65 yrs n=738	65-74 yrs n=465	75-84 yrs n=145	85+ yrs n=5
Total (any AEs)	406 (55.01)	267 (61.72)	92 (63.45)	2 (40.00)
Fatal	3 (0.41)	1 (0.22)	3 (2.07)	0
Serious	49 (6.64)	43 (9.25)	19 (13.10)	0
Withdrawal	36 (4.88)	25 (5.38)	19 (13.10)	0
CNS (confusion/extrapyramidal)	1 (0.14)	1 (0.22)	0	0
AE related to falling	3 (0.41)	5 (1.08)	2 (1.38)	0
Major CV events	2 (0.27)	1 (0.22)	3 (2.7)	0
Cerebrovascular events	3 (0.41)	6 (1.29)	1 (0.69)	0
Infections	197 (26.69)	156 (33.55)	37 (25.52)	1 (20.00)

Source: [SCS Appendix 5 - Table HA-saf-19]

Effect of gender

Female patients tended to report adverse events more frequently than male patients. Overall and for the three most frequent SOCs, when adjusting for the frequencies in the placebo group, there was no clear indication that NVA237 had a significantly different adverse event profile in women than in men although the difference between NVA237 and placebo in favour of NVA237 was less in female patients.

The proportion of patients with AEs on NVA237 and placebo were 56.6% and 65.2% in males and 68.8 and 70.8% in females, respectively. Of all AEs reported on NVA237 in the female group 12% (24 of 204) had a placebo-corrected difference in the frequency of AEs of 0.5% or more compared to the male group and of the male group 2% (6 of 341) had a placebo-corrected difference in the frequency of 0.5% or more compared to the female group. This indicates similar AE profile across gender.

The following AEs were >1% more frequent in females than in males: influenza-like symptoms, musculoskeletal pain, nasopharyngitis, rhinitis and urinary tract infection. In males only dry mouth was more than one per cent more frequent than in females. Atrial fibrillation was also more frequent in males than in females.

Effect of race

Caucasian patients constituted the vast majority of patients. There were a much smaller proportion of Asian patients and a very limited number of patients representing other races. Overall, there is no suggestion of an effect of race in the adverse event profile of NVA237, but this conclusion is limited because of the predominance of Caucasian patients.

Safety related to drug-drug interactions and other interactions

In vitro studies showed that NVA237 is unlikely to inhibit or to induce the metabolism of other drugs, as well as processes involving drug transporters. Metabolism plays a secondary role in the elimination of NVA237 and multiple enzymes are involved. Inhibition or induction of metabolism of NVA237 is unlikely to result in a relevant change of NVA237 exposure.

In clinical pharmacokinetic studies, no clinically relevant interaction was observed when NVA237 was administered concomitantly with indacaterol, an inhaled beta 2-adrenergic agonist, or cimetidine, an orally given inhibitor of the organic cation transport in the kidneys.

Discontinuation due to adverse events

With regard to the Core 6-month Safety database, discontinuations due to AEs were lower in the NVA237 group (6.0%) and tiotropium group (6.0%) compared to the placebo group (8.2%). The most frequently reported AE leading to discontinuation of study drug by preferred term was COPD (NVA237 1.7%, placebo 3.6%, and tiotropium 3.0%). Myocardial infarction was reported in 0.2% of patients (2 patients) in the NVA237 group and 0.4% of patients (1 patient) in the tiotropium group; no cases were reported in the placebo group.

The frequency of atrial fibrillation leading to discontinuation of study drug was 0.28% in the NVA237 group; this AE was not reported in the placebo or tiotropium groups.

With regard to the Core 12-month Safety database, discontinuations due to AEs were less frequent in the NVA237 group (8.0%) and tiotropium group (7.5%) compared to the placebo group (11.6%). The most frequently reported AE leading to discontinuation of study drug by preferred term was COPD (NVA237 1.9%, placebo 4.9%, and tiotropium 3.7%).

The frequency of the AE of atrial fibrillation (preferred term) leading to discontinuation of study drug was 0.2% (1 patient) in the NVA237 group; this AE was not reported in the tiotropium or placebo groups.

Post marketing experience

There are no post-marketing surveillance data available for NVA237 for the target indication of COPD.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The overall incidence of adverse events (in the 6-month database) as well as a number of adverse events related to COPD/symptoms of COPD in the NVA237 group does not raise concerns. It appears evident that dry mouth is truly an adverse drug reaction related to NVA237 taking the pharmacological mode of action into consideration. Other anticholinergic adverse events appear to be more frequent in the NVA237 (and the tiotropium) group than in the placebo group, although in small numbers.

Atrial fibrillation when reported as an adverse event occurred more frequently among NVA237-treated patients than in patients on placebo. However, when looking at adjudicated ECG recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was similar for NVA237 and placebo. Nevertheless, information has been added to the SmPC and included in the RMP as a potential risk.

In view of the potential risk of adverse cardiovascular outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the concerns on cardiovascular safety of same class products, adverse CV outcomes should be followed closely in the post-marketing setting. Consequently, the CHMP requested a Post-Authorisation Safety Study (PASS) to monitor cardiovascular and cerebrovascular outcomes post-marketing. The objective of this study will be to assess the relative risks of specific cardiovascular and cerebrovascular outcomes among new users of inhaled glycopyrronium compared to new users of non-NVA237 comparator drugs.

Additionally, the CHMP requested a Drug utilisation study to quantify the subpopulation with cardiovascular co-morbidity and to identify patient groups with missing information in the RMP. Missing information include prevalence of unstable angina, arrhythmia and long QT-syndrome in NVA237 users. This will be a multinational, multi-database drug utilisation study of inhaled glycopyrronium in

Europe. There is no indication that any of the death cases in the development programme are causally related to treatment with NVA237.

The frequency and nature of serious adverse events are generally considered to be typical for a moderate to severe COPD population. With the possible exception of atrial fibrillation, there is no indication that the reported serious adverse events are causally related to NVA237 treatment.

The laboratory findings are satisfactory with no clinically relevant findings.

In terms of special populations, there is no clear tendency that elderly patients experienced adverse events more frequently than younger patients, although the number of patients in the 75+ years group is low. Regarding gender, female patients tended to report adverse events more frequently than male patients. However, when adjusting for the frequencies in the placebo group, there is no clear indication that NVA237 has a significantly different adverse event profile in women than in men. There is no suggestion of an effect of race in the adverse event profile of NVA237, although there was a predominance of Caucasian patients.

2.6.2. Conclusions on the clinical safety

No major concerns were identified with regard to the safety of NVA237. The adverse events observed were typical of a moderately to severely affected COPD population. As expected from the pharmacological profile of NVA237, a number of anticholinergic adverse events appeared to be causally related to the use of NVA237, in particular dry mouth, but generally the excess numbers were low.

Atrial fibrillation when reported as an adverse event occurred more frequently among NVA237-treated patients than in patients on placebo. However, when looking at adjudicated ECG recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was similar for NVA237 and placebo. Nevertheless, information has been added to the SmPC and included in the RMP as a potential risk.

In view of the potential risk of adverse cardiovascular outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the concerns on cardiovascular safety of same class products, adverse CV outcomes should be followed closely in the post-marketing setting. Consequently, the CHMP requested a Post-Authorisation Safety Study (PASS) to monitor cardiovascular and cerebrovascular outcomes post-marketing.

On top of the above-mentioned PASS, cardio- and cerebrovascular events will be monitored through routine pharmacovigilance including cumulative analysis in PSUR and a multinational, multi-database drug utilisation study of inhaled glycopyrronium in Europe. Taking the above-information into account, the CHMP considers the following measures necessary to address issues related to safety:

- Post-authorisation safety study on cardio- and cerebrovascular outcomes (Multinational database cohort study to assess adverse cardiovascular outcomes in association with inhaled glycopyrronium in Europe)

- Drug utilisation study (Multinational, multi-database drug utilisation study of inhaled glycopyrronium in Europe).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 2. Summary of the risk management plan

Safety issue	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Important identified risks		
Narrow-angle glaucoma	Routine pharmacovigilance including cumulative analysis in PSUR. Targeted follow-up.	SmPC Section 4.4 Special warnings and precautions for use. NVA237 should be used with caution in patients with narrow angle glaucoma.
Bladder outflow obstruction and urinary retention	Routine pharmacovigilance including cumulative analysis in PSUR.	SmPC Section 4.4 Special warnings and precautions for use: NVA237 should be used with caution in patients with [….] urinary retention. Section 4.8 Undesirable effects.
Use in patients with severe renal impairment	Routine pharmacovigilance including cumulative analysis in PSUR.	SmPC Section 4.2 Posology and method of administration: NVA237 can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end stage renal disease requiring dialysis NVA237 should be used only if the expected benefit outweighs the potential risk Section 4.4 Special warnings and precautions for use: A moderate mean increase in total system exposure (AUClast) of up to 1.4 fold was seen in subjects with mild and moderate renal impairment and up to 2.2 fold in subjects with severe renal impairment and end stage renal disease. In patients with severe renal impairment (estimated glomerular filtration rate below 30 ml/min/1.73 m2), including those with end stage renal disease requiring dialysis, NVA237 should be used only if the expected benefit outweighs the potential risk. These patients should be monitored closely for potential adverse reactions. Section 5.2 Pharmacokinetic properties.
Important Potential risks		
Cardio- and cerebrovascular events	Routine pharmacovigilance including cumulative	SmPC Section 4.4 Special warnings and precautions for use: Patients with unstable ischemic heart disease, left ventricular failure,

	analysis in PSUR. Post-authorisation safety study on cardio- and cerebrovascular outcomes (Multinational database cohort study to assess adverse cardiovascular outcomes in association with inhaled glycopyrronium in Europe; n=3000) Drug utilisation study (Multinational, multi-database drug utilisation study of inhaled glycopyrronium in Europe; n=3000)	history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), a history of long QT syndrome or whose QTc (Fridericia method) was prolonged (>450 ms for males or >470 ms for females) were excluded from the clinical trials, and therefore the experience in these patient groups is limited. NVA237 should be used with caution in these patient groups. SmPC Section 4.8 Undesirable effects.
Atrial fibrillation	Routine pharmacovigilance including cumulative analysis in PSUR. Post-authorisation safety study on cardio- and cerebrovascular outcomes Drug utilisation study	SmPC Section 4.4 Special warnings and precautions for use: see above cardio- and cerebrovascular events. SmPC Section 4.8 Undesirable effects.
Paradoxical bronchospasm	Routine pharmacovigilance including cumulative analysis in PSUR.	SmPC Section 4.4 Special warnings and precautions for use: In clinical studies with NVA237, paradoxical bronchospasm was not observed. However, paradoxical bronchospasm has been observed with other inhalation therapy and can be life threatening. If this occurs, NVA237 should be discontinued immediately and alternative therapy instituted.
Medication error	Routine pharmacovigilance including cumulative analysis in PSUR.	"Information for the user" – "Instructions for use of inhaler"
Important missing information		
Use in patients with unstable ischemic heart disease, arrhythmia and long QT-syndrome	Routine pharmacovigilance. Drug utilisation study	For arrhythmia: SmPC Section 4.8 Undesirable effects, Section 5.1 Pharmacodynamic properties.
Use in patients with liver impairment	Routine pharmacovigilance. Drug utilisation study	SmPC Section 4.2 Posology and method of administration: No studies have been conducted in patients with hepatic impairment. NVA237 is predominantly cleared by renal excretion and therefore no major increase in exposure is expected in patients with hepatic impairment, Section 5.2 Pharmacokinetic properties.
Use in pregnancy and lactation	Routine pharmacovigilance Drug utilisation study	SmPC Section 4.6 Fertility, pregnancy and lactation.
Long-term use in COPD beyond 1 year	Routine pharmacovigilance	SmPC Section 4.8 Undesirable effects and Section 5.1 Pharmacodynamic properties.

	Drug utilisation study	
Off-label use in adults with asthma without COPD and in the pediatric population	Routine pharmacovigilance Drug utilisation study	SmPC Section 4.1 Therapeutic indications
Safety and efficacy of alternative dose regimens	Routine pharmacovigilance Post-authorisation efficacy study	SmPC Section 4.2 Posology and method of administration: The recommended dose is the inhalation of the content of one capsule once daily using the NVA237 inhaler.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Post-authorisation safety study on cardio- and cerebrovascular outcomes (Multinational database cohort study to assess adverse cardiovascular outcomes in association with inhaled glycopyrronium in Europe).	Proposed study protocol 3 months after market authorisation in Europe. Interim results 1 year after launch in Europe. Final report 5 years after launch.
Drug utilisation study (Multinational, multi-database drug utilisation study of inhaled glycopyrronium in Europe).	Proposed study protocol 3 months after market authorisation in Europe. Interim results 1 year after launch in Europe. Final report 3 years after launch.
Post-authorisation efficacy study (A 26-week treatment, multi-center, randomized, double-blind, parallel-group study to compare the efficacy, safety and tolerability of glycopyrronium given once and twice daily in patients with stable Chronic Obstructive Pulmonary Disease and moderate to severe airflow obstruction).	Proposed study protocol 6 months after market authorisation in Europe. Final study report 3 years after agreement with EMA on study protocol.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The benefits of NVA237 in the once-daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD) were adequately documented in a large non-clinical and clinical programme.

Clinically relevant differences to placebo were shown for lung function measurements, moderate and severe exacerbation rates and to a lesser extent also for symptomatic endpoints. In both pivotal studies, NVA237 showed statistically significant improvement in trough FEV_1 at week 12 compared with placebo. The treatment difference was 108 mL (95% CI: 78.5-136.8 mL) in Study A2304 and 97 mL (95% CI: 64.6-130.2 mL) in Study A2303.

Efficacy was also shown to be at least on par with tiotropium, the only currently marketed long-acting muscarinic antagonist.

Moreover, the efficacy shown in the short-term (12 weeks) appears to be maintained in the long-term (up to 52 weeks).

Uncertainty in the knowledge about the beneficial effects

The efficacy of the selected dose regimen (50 µg once daily) has been clearly demonstrated. In addition, the once daily regimen offers a benefit regarding patient compliance. However, the additional dose-finding study (A2208) seems to suggest that a twice daily regimen (such as 25 µg b.i.d. or 50 µg b.i.d.) could be more efficacious. In order to follow up, the CHMP requested a post-authorisation clinical study to further characterise the optimal dosing schedule for NVA237. "Optimal dosing schedule" was considered as important missing information at the time of Opinion and should be added in the RMP.

The effects on patient-reported symptomatic measures (SGQR and TDI) were not very large as the clinically significant differences expected to be found by the Applicant were either not met in SGQR in any of the pivotal studies or not met in TDI (Study A2303)) or borderline achieved (Study A2304). Both studies also document a modest, but relevant decrease in frequency of moderate and severe COPD exacerbations and improvement in terms of use of rescue medication in NVA 237-treated patients compared to placebo. However, the totality of the efficacy data from the pivotal studies (spirometry, exacerbations and patient-reported outcomes, use of rescue medication etc.) are considered to reflect a clinically relevant benefit in COPD patients.

Risks

Unfavourable effects

The adverse events observed in the clinical programme are considered to be typical of a moderately to severely affected COPD population. As expected from the pharmacological profile of NVA237 (an anti-muscarinic agent), a number of anticholinergic adverse events appeared to be causally related to the use of NVA237, in particular dry mouth. However, for most of the adverse events thought to be anticholinergic, the incidences in excess of placebo were low.

Uncertainty in the knowledge about the unfavourable effects

A higher frequency of adverse events of atrial fibrillation in NVA237-treated patients was observed. However, when looking at adjudicated ECG recordings, the number of patients with a new or worsening ECG finding of atrial fibrillation was similar for NVA237 and placebo. Atrial fibrillation is considered as a potential risk in the risk management plan and included in the SmPC.

Considering the potential risk of adverse cardiovascular (CV) outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the recent concerns on cardiovascular safety of same class products, adverse CV outcomes should be followed closely in the post-marketing setting. Consequently, the CHMP requested the conduct of a PASS to monitor these outcomes post-marketing; this is included in the risk management plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

The treatment difference in favour of NVA237 for the primary efficacy endpoint, FEV_1 at week 12, was approximately 100 mL. This difference can be considered clinically relevant. The relevance of the finding was supported by the generally consistent superiority of NVA237 to placebo on most other efficacy endpoints. Statistically significant improvement compared to placebo was also observed for patient-reported symptomatic endpoints, although the treatment effect was not large. Looking at the totality of the efficacy data (spirometry, exacerbations and patient-reported outcomes, use of rescue medication etc.), the CHMP concludes that the benefit of NVA 237 in COPD is modest, but clinically relevant.

The effects were similar to those of the long-acting muscarinic antagonist tiotropium. The adverse events observed are typical of a moderately to severely affected COPD population. As expected from the pharmacological profile of NVA237, a number of anticholinergic adverse events appear to be causally related to the use of NVA237, in particular dry mouth, but generally the excess numbers are low.

Considering the potential risk of adverse cardiovascular (CV) outcomes related to the mechanism of action of anticholinergic quaternary ammonium compounds and the concerns on cardiovascular safety of same class products, adverse CV outcomes will be followed up as explained above.

Benefit-risk balance

The favourable effects described above are considered important in that NVA237 improved objective lung function measurements compared to placebo and that these changes were accompanied by other improvements, including symptomatic improvements, in patients with COPD. Since the overall safety and tolerability profile is considered benign, the benefit-risk balance is considered positive.

Discussion on the benefit-risk balance

The efficacy of NVA237 50 µg once daily over placebo in terms of improvement in lung function measurements and relevant measures of symptomatic benefit has been documented in the two pivotal studies and is supported by a phase II study and a further phase III study. The currently proposed once daily regimen provides a clinical benefit on par with an already approved product within the same class and is associated with a relatively unproblematic safety and tolerability profile. In addition, the once daily regimen offers a benefit regarding patient compliance.

No major concerns were identified with regard to the safety of NVA237. The adverse events observed were typical of a moderately to severely affected COPD population. As expected from the

pharmacological profile of NVA237, a number of anticholinergic adverse events appeared to be causally related to the use of NVA237, in particular dry mouth, but generally the excess numbers were low.

Therefore, on the basis of quality, safety and efficacy data submitted, the CHMP considers that there is a favourable benefit-to-risk balance for NVA237.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Seebri Breezhaler in the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Post-authorisation safety study on cardio- and cerebrovascular outcomes (Multinational database cohort	Proposed study protocol 3 months after

study to assess adverse cardiovascular outcomes in association with inhaled glycopyrronium in Europe)	market authorisation in Europe. Interim results 1 year after launch in Europe. Final report 5 years after launch.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.