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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Division / Office	DPARP/ODEII/OND/CDER/FDA
Reviewer Name(s)	Erika Torjusen, MD, MHS
Review Completion Date	September 24, 2015
Established Name	Glycopyrrolate
(Proposed) Trade Name	Seebri Neohaler
Therapeutic Class	Anticholinergic
Applicant	Novartis
Formulation(s)	single dose dry powder for inhalation
Dosing Regimen	12.5 mcg BID
Indication(s)	long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
Intended Population(s)	Adults with COPD

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on my review of the risk-benefit assessment, my recommendation is **Approval** of glycopyrrolate (GP) 12.5 mcg twice daily for the treatment of chronic obstructive pulmonary disease (COPD), pending revisions to the label.

1.2 Risk Benefit Assessment

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

Glycopyrrolate has been on the market in other formulations for indications different from COPD for over 40 years, with a well-known safety profile.

(b) (4)

The development of the GP 12.5 mcg BID dose and dose regimen were chosen to support the US submission, based on the results of the dose ranging study A2208. This study was conducted following discussion with the FDA to investigate QD and BID dosing regimens.

To support the proposed indication, the Applicant submitted data from one dose ranging/regimen study (A2208) and two replicate 12-week confirmatory trials (A2317 and A2318). Study A2208 was a 28-day randomized, double blind, placebo-controlled, crossover, dose ranging study of glycopyrrolate (GP) in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Studies A2317 and A2318 were replicate, phase 3, 12-week, randomized, double-blind, placebo-controlled, multicenter studies to assess the efficacy and safety of GP 12.5 mcg BID versus placebo in patients with moderate to severe COPD. Studies (A2317 and A2318) enrolled a total of 873 COPD patients; 438 to GP 12.5 mcg BID and 435 to placebo. Additional supportive efficacy was provided by studies A2336 and A2337 which were conducted as part of the combination GP/Indacaterol development program and included single-ingredient GP treatment arms as part of the typical factorial design.

The primary endpoint in the replicate phase 3 studies (A2317 and A2318) was FEV1 AUC(0-12h) at Week 12. The LS mean treatment difference for change from baseline in FEV1 AUC(0-12h) was statistically significant for GP versus placebo at 12 weeks (0.139 L and 0.123 L, $p<0.001$, respectively) for both studies (A2317 and A2318).

The secondary endpoint SGRQ, when analyzed via a responder analysis, where a response was defined as those patients who achieved and MCID $\geq$-4, GP did not demonstrate a statistically

significant effect vs. placebo (OR: 1.43, 95% CI [0.95, 2.15]) in study A2317. In study A2318, the responder analysis, showed that GP demonstrated a statistically significant effect vs. placebo (OR: 1.78, 95% CI [1.17, 2.71]).

The assessment of risk is based on 3-month data from 4 studies; A2317, A2318, A2336, and A2337. Studies A2336 and A2337 were conducted as part of the combination GP/Indacaterol development program, and each included single-ingredient GP treatment arms as part of the typical factorial design. The single-ingredient GP and corresponding placebo arms from these trials were also included in the GP safety database. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of GP received (12.5 mcg). Safety assessments in these 4 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long term safety study, A2319, was conducted and did not reveal any additional safety signals.

The 3-month safety database included 1,889 COPD patients; 951 treated with GP 12.5 mcg BID and 938 patients treated with placebo. Few patients discontinued from the studies, with more patients discontinuing in the placebo group (88% placebo vs. 92% GP treated patients completed the study). Deaths were infrequent in the clinical development program (n=3 (0.3%), GP vs. n=2 (0.2%) placebo).

The overall occurrence of serious adverse events (SAEs) was low and equally distributed across treatment groups [n=38 (4.1%), placebo vs. n=40 (4.2%) GP]. SAEs that were reported more frequently in the GP group as compared with placebo were infection [n=5 (0.5%) placebo, vs, n=8 (0.8%) GP], neoplasms [n=2 (0.2%), placebo vs. n=4 (0.7%), GP], general and administration site disorders [n=0, placebo vs. n=3 (0.3%) GP], renal and urinary disorders [n=1 (0.1 %), placebo vs. n=2 (0.2 %), GP], vascular disorders [n=0, placebo vs. n=2 (0.2%), GP] and skin disorders [n=0, placebo, n=1 (0.1%), GP]. Overall, SAEs occurred infrequently in the clinical development program, with slight, but clinically insignificant numerical imbalances.

AEs leading to discontinuation were more frequent in the placebo patients (4.1%) compared to (2.5%) in the GP treated patients. COPD-related events such as COPD exacerbations were the most common reason for discontinuation (1.6% placebo vs. 1.0% GP).

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs. The AESIs that occurred more frequently in the GP treated group were the following: bladder outflow obstruction and urinary retention (0.1% placebo, 0.3% GP) and atrial fibrillation/flutter events (0.8% placebo, 1.7% GP). In addition to the AESI, the Applicant conducted a review of major adverse cardiovascular events (MACE) which have been a historical concern with this drug class. MACE events occurred more frequently in the placebo group (0.6%) compared to the GP-treated patients (0.4%).

Patients experiencing at least one adverse event were fairly balanced between the placebo and GP treatment groups (42.5% placebo, 44.2 % GP). Common adverse reactions that occurred in at least 1% in any treatment group and more were more common in the GP treated group included: upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, sinusitis, and urinary tract infection. The findings from the 12-month safety study were consistent with the results seen for the primary 3 month safety database. No new safety signal was identified.

Based on the efficacy and safety findings, the risk-benefit assessment supports the Approval of glycopyrrolate for COPD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarket requirements or commitments are recommended at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

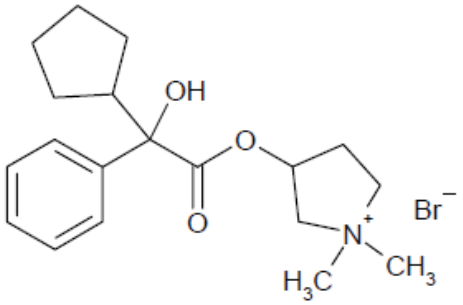
Glycopyrrolate (GP) 12.5 mcg inhalation powder hard capsule contains glycopyrronium bromide as the active drug substance. GP is an antagonist at muscarinic acetylcholine receptors. In vitro assays have demonstrated that GP is a competitive antagonist at all five human muscarinic receptor subtypes (M1-M5) and displays some selectivity for the M3 over the M2 receptor. One GP 12.5 mcg inhalation powder hard capsule contains 15.6 mcg of glycopyrronium bromide (glycopyrrolate) corresponding to 12.5 mcg of glycopyrronium base. GP has been formulated as a 12.5 mcg inhalation white powder in a transparent orange hypromellose hard capsule for inhalation administration using the Concept1 device for the treatment of chronic obstructive pulmonary disease. This device is already approved and marketed (as the Neohaler), and was reviewed in a previous review cycle (as part of NDA 022383 for Arcapta) (see Figure 2).

Glycopyrrolate/Indacaterol 12.5/27.5 mcg (GPI) delivered via the Neohaler device was submitted in NDA 207-930 with the same indication that is proposed for GP.

Each transparent orange HPMC capsule contains 15.6 mcg of glycopyrrolate blended with approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein) and 0.04 mg of magnesium stearate.

Glycopyrrolate, the active component of Seebri Neohaler, is chemically described as 3-[(cyclopentylhydroxyphenylacetyl) oxy]-1,1-dimethylpyrrolidinium bromide. This synthetic quaternary ammonium compound acts as a competitive antagonist at muscarinic acetylcholine receptors, also referred to as anticholinergic. GP, C19H28BrNO3, is a white powder with low solubility in water and alcohol and molecular mass of 398.33. The structural formula is:

Figure 1. Drug Structure



Source: GP Proposed Product Label

The Neohaler device is an inhalation device used to inhale the dry powder within the Seebri capsule Figure 2. The amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow rate and inspiratory time. Under standardized in vitro testing at a fixed flow rate of 90 L/min for 1.3 seconds, the Neohaler device delivered 13.1 mcg for the 15.6 mcg dose strength (equivalent to 12.5 mcg of glycopyrronium) from the mouthpiece. This in vitro testing revealed that the Neohaler device had a specific resistance of 0.07 cm H2O1/2/L/min. Peak inspiratory flow rates (PIFR) achievable through the Neohaler device were evaluated in 26 adult patients with COPD of varying severity. Mean PIFR was 95 L/min (range 52 to 133 L/min) for adult patients. Twenty-five of 26 patients (96%) in this study generated a PIFR through the device exceeding 60 L/min.

Figure 2. Neohaler Device

Source: Module 3.2.P.7, Figure 4-1, page 6

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Available treatments for COPD

Class		Generic Name	Brand Name
Beta2-adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair autoinhaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol Solution	Perforomist
		Indacaterol maleate	Arcapta Neohaler
Anticholinergics		Ipratropium bromide	Atrovent HFA
		Tiotropium bromide	Spiriva Handihaler and Spiriva Respimat
		Aclidinium bromide	Tudorza Pressair
Combination	SABA/anti-cholinergic	Albuterol/Ipratropium	Combivent
		Albuterol/Ipratropium	Combivent Respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
		Budesonide/Formoterol	Symbicort
		Fluticasone/Vilanterol	Breo Ellipta
Xanthines		Theophylline	Multiple
Phosphodiesterase Inhibitors	PDE4 Inhibitor	Rofumilast	Dalisresp

*Not specifically approved for COPD

2.3 Availability of Proposed Active Ingredient in the United States

Glycopyrrolate is available in tablet form as Robinul (1mg) and Robinul Forte (2mg), as well as an injection solution.

2.4 Important Safety Issues With Consideration to Related Drugs

Class effects of anticholinergics include worsening of narrow angle glaucoma and worsening of urinary retention.

The Agency has also historically been concerned with the cardiovascular safety of these agents. The concerns have been discussed extensively both in the medical literature and in open public

forums (November 2009 FDA Allergy Drugs Advisory Committee Meeting). As a result of these concerns, the Agency released Early Communications on March 18, 2008 and October 7, 2008 about the ongoing safety review of Spiriva HandiHaler (SHH) that described these observations. Following the Early Communication, Boehringer Ingelheim submitted data from a 6,000 patient, 4-year study with the SHH [Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT[1], trial 205.235)] which was analyzed by the Agency and discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) in November of 2009. As a result, in January 2010 the Agency provided a Follow-Up to the previous Early Communications regarding the safety of tiotropium marketed as the SHH. In this update, the Agency communicated its conclusion that the available data, including results from UPLIFT do not support an association between the use of SHH (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. Additional evaluation of tiotropium was conducted by Boehringer Ingelheim in the TIOSPIR[2] (Tiotropium Safety and Performance in Respimat) trial after clinical trials data showed that tiotropium 5 mcg delivered via the Respimat inhaler showed more deaths reported compared to placebo. The trial involved over 17,000 COPD patients with a mean follow up period of 2.3 years and concluded that Spiriva Respimat 5 mcg or 2.5 mcg had a safety profile and exacerbation efficacy similar to that of Spiriva HandiHaler 18 mcg in patients with COPD.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Key Regulatory Interactions with the Agency

- July 15, 2008, EOP2 Type B: The sponsor proposed [redacted] (b) (4) GP for phase 3 trials, however, the Division advised the Applicant to further evaluate the dose and dosing interval because the data submitted did not fully characterize the optimal dose of GP for progression into phase 3. The Division specified the following shortcomings that should be addressed in identifying and justifying an optimal dose: [redacted] (b) (4) ; data better clarifying both GP peak and trough effects should be collected; duration of effect data (i.e., 24-hour profiles) should be more comprehensive.

- May 4, 2009, Type A (TCON): Clarifications were provided after a "No Agreement" letter was issued on March 26, 2009 for a Special Protocol Assessment (SPA). The Division clarified and reiterated that [redacted] (b) (4) The Division requested that sponsor provide more data regarding the dosing interval and that the sponsor explore lower dose(s) to provide convincing evidence of the appropriate dose and dosing interval. Dosing intervals and

dose ranges must be explored out to 28 days duration in order to determine the lowest effective dose of GP.

- July 13, 2009, Type A: Post SPA denial meeting (letter dated May 21, 2009). The Division stated that [redacted] (b) (4)
  The results in protocol A2206 suggest that the trough FEV_1 response may increase through Day 28. Further, more frequent dosing regimens have not been explored, which might identify a lower total daily dose of GP with optimum benefit. The Division encouraged the sponsor to explore lower doses and alternative regimens out to 28 days to provide convincing evidence of the appropriate dose and dosing interval.

- January 29, 2010, EOP2A Type B: The Division recommended that Novartis look at various dosing intervals early in the development plan to establish the optimal dosing regimen [redacted] (b) (4).

- September 28, 2011, Pre-NDA Type B: Further discussion regarding dose selection for phase 3 trials. The Applicant proposed [redacted] (b) (4).

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately indexed and complete to permit review. The clinical site inspections have been completed and No Official Action is indicated.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in this NDA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 48655 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below:

Covered Clinical Studies (Name and/or Number): A1302, A2110, A2205, A2206, A2208, A2303, A2304, A2310, A2314, A2316, A2317, A2318, A2319

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 4981		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

No clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis; multiple investigators used in the studies and double-blind placebo controlled trials. One investigator disclosed receiving financial compensation in excess of $50,000 in honoraria for speaking programs, travel expenses and consulting activities. However, given the international scope of this development program, this was unlikely to have affected the overall results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Glycopyrrolate (GP) 12.5 mcg inhalation powder hard capsule contains glycopyrronium bromide as the active drug substance. GP is an antagonist at muscarinic acetylcholine receptors. In vitro assays have demonstrated that GP is a competitive antagonist at all five human muscarinic receptor subtypes (M1-M5) and displays some selectivity for the M3 over the M2 receptor. One GP 12.5 mcg inhalation powder hard capsule contains 15.6 mcg of glycopyrronium bromide (glycopyrrolate) corresponding to 12.5 mcg of glycopyrronium base. GP has been formulated as a 12.5 mcg inhalation white powder in a transparent orange hypromellose hard capsule for inhalation administration using the Concept1 device for the treatment of chronic obstructive pulmonary disease. This device is already approved and marketed (as the Neohaler), and was reviewed in a previous review cycle (as part of NDA 022383 for Arcapta) (see Figure 1).

Glycopyrrolate/Indacaterol 12.5/27.5 mcg (GPI) delivered via the NeohalerTM device was submitted in NDA 207-930 with the same indication that is proposed for GP.

Each transparent orange HPMC capsule contains 15.6 mcg of glycopyrrolate blended with approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein) and 0.04 mg of magnesium stearate.

The starting materials and their specifications are adequate to control drug substance quality. Reagents and (b) (4) are adequately controlled with regard to their purity. Proposed (b) (4) methods are acceptable. The provided process development information adequately supports the commercial process. Characterization is sufficient to unequivocally support the proposed structure. There is a very low amount of impurities in the drug substance.

The Chemistry, Manufacturing, and Controls review was pending at the time of this review. For a more in depth review of the CMC related issues, see the review written by Arthur Shaw, PhD.

4.2 Clinical Microbiology

The drug product is not a sterile product. Manufacturing of the inhalation powder hard capsule takes place in [redacted] (b) (4). The inhalation powder hard capsules are submitted to microbiological release testing.

The microbial attributes of the drug product were assessed through development studies and as part of the long-term registration stability testing. All microbial attributes are consistently met to date on all batches as provided in [3.2.P.8.1].

The recommendation from Clinical Microbiology is Approval. No Clinical Microbiology issues were identified. For a more in depth review of the clinical microbiology related issues, see the review written by Vinayak Pawar, Ph.D.

4.3 Preclinical Pharmacology/Toxicology

The sponsor Novartis has conducted adequate nonclinical safety evaluations to support the approval of Seebri Neohaler from the nonclinical perspective. Nonclinical studies included pharmacology, safety pharmacology, ADME, general toxicology, genotoxicity, carcinogenicity, and reproductive toxicology. There are no outstanding nonclinical issues at this time.

The safety pharmacology of GP was assessed in studies of the central nervous system (CNS), cardiovascular system, and respiratory system. There were no dose limiting effects noted in CNS or respiratory parameters. Cardiovascular effects were observed, including transient tachycardia at doses equal to and greater than 0.01 mg/kg, and increased diastolic arterial blood pressure at 0.1 mg/kg GP. Mydriasis and dryness of mucous membranes were observed, and is an expected pharmacological effect of GP.

The half-lives of GP in mice, rats, and dogs were 3.9, 23, and 4.4 hrs, respectively. The plasma protein binding in rats, dogs, and humans ranged from 23-41%. Studies in mice, rats, and dogs suggest distribution in extravascular tissues, with moderate to strong clearance. Following IV administration in mice, the longest half-live values were noted in the epididymis, eye choroid, eye, fat (brown), Harderian gland, kidney (cortex), and liver. Following IV administration in rats, the longest half-live values were noted in the kidney and liver.

The pivotal general toxicology studies supporting the safety of GP were a 26-week study in rats, and 39-week study in dogs. In the 26-week inhalation toxicology study (with a 4 week recovery), three doses were tested (0.09, 0.67, and 4.98 mg/kg GP (salt). The target organs of toxicity were

the eyes, lungs (epithelial hypertrophy), seminal vesicles (inflammation), and urinary bladder (inflammation). Bilateral and unilateral lenticular changes were observed at the mid- and high-doses in both sexes, and were partially reversible. These changes were characteristic of muscarinic receptor inhibition. The NOAEL was noted to be the low dose.

In the 39 week inhalation toxicology study (with a 4 week recovery period), beagle dogs were dosed with 0 (air), 0 (vehicle: 1% magnesium stearate, 99% lactose monohydrate), 0.031/0/028, 0.12/0.11, 0.33/0.32 mg/kg, (male/female, estimated achieved doses in salt form). The targets organs of toxicity were the pharynx (inflammation, ectasia of the ducts and/or alveoli), lacrimal gland (hypertrophy), and mandibular salivary glands (hypertrophy). All findings reversed after the recovery period. The NOAEL was determined as the low dose, but due to findings being clinically monitorable and/or not dose limiting, the supporting dose was determined to be the high dose.

Regarding genetic toxicology, GP was negative in genetic toxicology testing based on results from the in vitro bacterial reverse mutation assay, in vitro human lymphocyte chromosomal aberration assay, and in vivo rat micronucleus test.

Carcinogenicity assessments were performed in a traditional 2-year bioassay in rats, and a 26 week bioassay in transgenic mice (Tg.rasH2 mice). Both bioassays were negative for test-article related tumors.

The standard battery of reproductive and developmental toxicity studies were completed with GP in rats and rabbits. Conclusions regarding these studies are pending and will be discussed in the non-clinical review by Jane Sohn, PhD.

Embryofetal development was investigated in gravid rats and rabbits. GP was negative for teratogenicity. Overall, there were no teratogenic or non-teratogenic findings with GP.

Conclusions: The applicant has a complete nonclinical pharmacology and toxicology program for GP under NDA 207923. Therefore, there is adequate nonclinical support for the safety of the proposed clinical dose doses of GP.

For further details regarding the non-clinical review, refer to the full review by Jane Sohn, PhD

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

GP is an antagonist at muscarinic acetylcholine receptors. In vitro assays have demonstrated that GP is a competitive antagonist at all five human muscarinic receptor subtypes (M1-M5) and displays some selectivity for M3 over the M2 receptor.

4.4.2 Pharmacodynamics

The pharmacokinetic properties of GP were characterized in healthy subjects and in COPD patients after BID, single QD and repeated QD dosing. The bronchodilator effect profile of GP was assessed in COPD patients in A2317, A2318, and in the dose ranging studies A2205 and A2208. Cardiac effects of high doses of GP were assessed in COPD patients in A2206 and in healthy volunteers in the thorough QT A2110 and following single i.v. dosing in A2108. Supplementary information is provided from A2105 which investigated cardiac effects of GPI and used GP as one comparator.

4.4.3 Pharmacokinetics

The pharmacokinetics of GP after repeated once daily inhalation were investigated in A2103 and a pooled population pharmacokinetic analysis was performed to characterize the GP pharmacokinetics in COPD patients after inhalation of GP 12.5 mcg BID. Generally the PK characteristics in COPD patients was consistent with the data from healthy subjects, namely the pharmacokinetics of GP were linear and dose proportional.

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

Absorption: Following oral inhalation using the Seebri Neohaler inhaler, GP was rapidly absorbed and reached peak plasma levels at 5 minutes post dose.

The absolute bioavailability of GP inhaled via Seebri Neohaler was estimated to be about 40%. About 90% of systemic exposure following inhalation is due to lung absorption and 10% is due to gastrointestinal absorption.

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

Distribution: After intravenous administration, the steady-state volume of distribution of GP was 83 L and the volume of distribution in the terminal phase was 376 L. The in vitro human plasma protein binding of GP was 38% to 41% at concentrations of 1 to 10 ng/mL.

Metabolism: In vitro metabolism studies show GP hydroxylation resulting in a variety of mono-and bis-hydroxylated metabolites and direct hydrolysis resulting in the formation of a carboxylic acid derivative (M9). Further in vitro investigations showed that multiple CYP isoenzymes contribute to the oxidative biotransformation of GP and the hydrolysis to M9 is likely to be catalyzed by members from the cholinesterase family pre-systemically and/or via first pass metabolism from the swallowed dose fraction of orally inhaled GP.

Elimination:

Renal elimination of parent drug accounts for about 60% to 70% of total clearance of systemically available GP whereas non-renal clearance processes account for about 30% to 40%. Biliary clearance

contributes to the non-renal clearance, but the majority of non-renal clearance is thought to be due to metabolism.

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

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

Drug Interactions: In vitro inhibition studies demonstrated that GP has no relevant capacity to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4/5, the efflux transporters MDR1, MRP2 or MXR, and the uptake transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT2. In vitro enzyme induction studies did not indicate a clinically relevant induction by GP for any of the cytochrome P450 isoenzymes tested as well as for UGT1A1 and the transporters MDR1 and MRP2.

In a clinical study in healthy volunteers, cimetidine, an inhibitor of organic cation transport which is thought to contribute to the renal excretion of GP, increased total systemic exposure (AUC) to GP by 22% and decreased renal clearance by 23%.

Special Populations: Population pharmacokinetic analysis showed no evidence of a clinically relevant effect of age (40 to 85 years) or body weight (45 to 120 kg) on systemic exposure to GP. In addition, there was no evidence of a clinically significant ethnic/race effect (across Caucasian, Chinese, Hispanic/Latino, Japanese subjects). Gender, smoking status, and baseline FEV_1 have no apparent effect on maximal or average GP systemic exposure.

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

Hepatic Impairment: The effects of hepatic impairment on the pharmacokinetics of GP have not been studied. GP is cleared predominantly from systemic circulation by renal excretion

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2. Sources of Clinical Data

Study ID *Dates*	Design	Study Duration	Treatment Arms	N	Population	Endpoint	Sites *% US Sites*
Dose-Ranging/Dose Regimen (Phase 2)							
A2208 *Apr 2010-Dec 2010*	R, DB, PC, MC, 2 period, incomplete block, CO Dose finding	28 days	GP 12.5 mcg QD GP 25 mcg QD GP 12.5 mcg BID GP 50 mcg QD GP 25 mcg BID GP 100 mcg QD GP 50 mcg BID Pbo BID	89 96 96 92 96 96 87 91	moderate to severe COPD	Trough FEV_1	Belgium, Germany, Hungary, India, Netherlands, Poland, Romania, Spain, US *21%*
Confirmatory (Phase 3)							
A2317 *Nov 2012-Oct 2013*	R, DB, PC, MC Safety/ Efficacy	12 wks	GP 12.5 mcg BID Pbo BID	222 219	moderate to severe COPD	FEV_1 AUC_{0-12h}	US *100%*
A2318 *Nov 2012-Dec 2013*	R, DB, PC, MC Safety/ Efficacy	12 wks	GP 12.5 mcg BID Pbo BID	216 216	moderate to severe COPD	FEV_1 AUC_{0-12h}	US *100%*
Supportive Phase 3 Studies							
A2336 *Nov 2012-Feb 2014*	R, DB, PG, PC, AC, MC Safety/ Efficacy	12 wks	Ind/GP 12.5/27.5 mcg BID Ind 27.5 mcg BID GP 12.5 mcg BID Pbo BID	260 260 261 261	moderate to severe COPD	FEV_1 AUC_{0-12h}	Canada, Spain, Philippines, Poland, Romania, Ukraine, US, Vietnam *49%*
A2337 *Dec 2012-Feb 2014*	R, DB, PG, PC, AC, MC Safety/ Efficacy	12 wks	Ind/GP 12.5/27.5 mcg BID Ind 27.5 mcg BID GP 12.5 mcg BID Pbo BID	250 251 251 249	moderate to severe COPD	FEV_1 AUC_{0-12h}	Colombia, Egypt, France, Guatemala, Hungary, Panama, Slovakia, Slovenia, US *60%*

Table 2. Sources of Clinical Data

Study ID *Dates*	Design	Study Duration	Treatment Arms	N	Population	Endpoint	Sites *% US Sites*
Long Term Safety Study							
A2319 *Oct 2012-Nov 2014*	R, DB, PG, AC, MC Safety	52 wks	GP 12.5 mcg BID Ind 75 mcg QD	251 256	moderate to severe COPD	AEs (evaluated lung function)	US *100%*

Source CSR and Section 5.2 tabular listing of clinical trials

R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, OL=open label, AC=active control, MC= multicenter, BID=twice daily, QD: once daily, GP = glycopyrrolate, Ind= indacaterol, Pbo= placebo, COPD=chronic obstructive pulmonary disease, AEs=adverse events
Source: CSR A2205, A2208, A2317, A2318, A2336, A2337, A2319

5.2 Review Strategy

The focus of this review is the efficacy and safety of GP 12.5 mcg BID. Study A2208 was the dose range/regimen finding study which examined doses various QD and BID doses.

This clinical review focuses on 5 randomized, double-blind, placebo-controlled studies: the phase 2 dose-ranging study (A2208), two confirmatory phase 3 studies (A2317 andA2318) and two supportive studies (A2336, and A2337). The active-controlled long-term safety study A2319 did not reveal any new safety findings and is consistent with the safety findings from the two confirmatory phase 3 trials. Any differences noted in the long-term safety trial as compared to the placebo-controlled safety database will be noted in Section 7 of this review.

Section 5.3 Discussion of Individual Studies/Clinical Trials, describes the protocols in detail for each individual study. Section 6 Review of Efficacy, reviews the efficacy results for each individual study. This section includes efficacy results from all treatment arms of A2317 and A2318. Supportive efficacy information is provided from the GP monotherapy treatment arms in Studies A2336 and A2337, conducted in support of the GP/Ind clinical development program. Section 7 Review of Safety, describes pooled safety for the two pivotal phase 3 trials (A2317 and Study A2318) as well as the GP and placebo arms for the two supportive phase 3 trials (A2336 and A2337). The results of the long-term safety study (A2319) are consistent with the results in the pivotal 3 month trials and are discussed in the relevant sections when additional data provides clarification.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Studies A2317 and A2318

Study A2317 and A2318 were identically designed trials. The following section outlines the protocol for these studies.

Administrative Information

Study A2317

- **Study title**: A 12-week multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of GP in moderate to severe COPD patients
- **Study dates:** Nov 13, 2012- Oct 11, 2013
- **Study sites:** 55 centers in the USA
- **Study report date:** April 11, 2014

Study A2318

- **Study title**: A 12-week multi-center, randomized, double-blind, placebo controlled study to assess the efficacy and safety of GP in moderate to severe COPD patients
- **Study dates:** Nov 26, 2012- Dec 26, 2013
- **Study sites:** 64 centers in the USA
- **Study report date:** August 22, 2014

Objectives/Rationale

Primary Objectives

- The primary objective was to demonstrate superiority of GP 12.5 mcg BID versus placebo with respect to the standardized area under the curve (AUC) for forced expiratory volume in one second (FEV1) between 0 - 12 h post dosing (FEV1 AUC 0-12h) at Week 12 of treatment in moderate to severe COPD patients

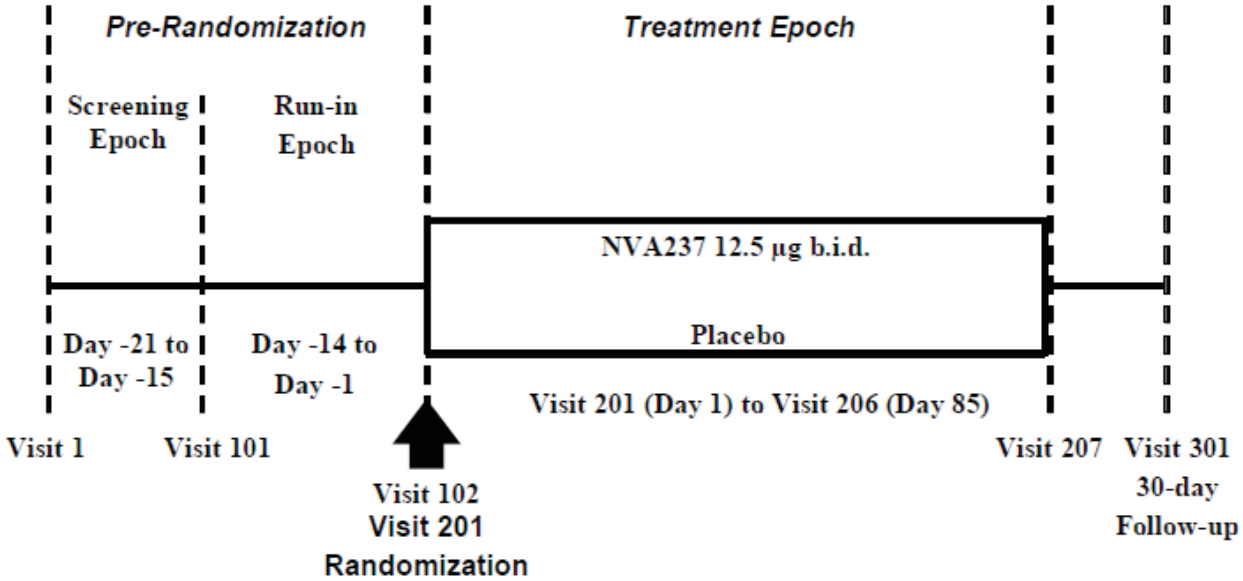
Study Design and Conduct

Overview
Studies A2317 and A2318 were replicate, phase 3, 12-week, randomized, double-blind, placebo-controlled, multicenter studies of GP 12.5 mcg BID versus placebo in patients with moderate to severe COPD.

The studies consisted of a screening epoch, a 14-day run-in epoch, a baseline/randomization visit, a 12-week treatment epoch (GP 12.5 mcg BID or placebo), followed by a study completion evaluation and a follow-up epoch of 30 days.

The study design for both studies is depicted in Figure 3.

Figure 3. Study Design: Studies A2317 and A2318



NVA237=GP
Source: Module 5.3.5.1 CSR A2317, Figure 9-1, Page 44, Module 5.3.5.1 CSR A2318, Figure 9-1, Page 45

The schedules of assessments is shown in

Table 3.

APPEARS THIS WAY ON ORIGINAL

Table 3. Schedule of Assessments: Studies A2317 and A2318

Epoch	Screen	Run-In		Treatment									Follow-up
Visit Number	1	101	102*	201*	202	203	204	205	206	207	UV	299	301
Visit	Screening (visit 1)	Run-in (visit 101)	Run-in Visit Part of Day 1	Randomization Visit 201						Study Termination	Treatment Discontin.	Premat. Study Withdrawal	Safety Follow-up
Week	-3 to -2	-2	1	1	1	2	4	8	12	12	---	---	---
Day	-21 to -15	-14	1*	1*	2	15	29	57	85	86	---	---	+30[7]
Obtain informed consent	X												
Demographics	X												
Relevant Medical History[1]	X	X	X										
History of CV risk factors	X												
History of pulmonary diseases	X												
COPD exacerbation history	X												
Smoking history	X												
Smoking status			X						X		X	X	
Re-screening	X												
Eligibility (Inclusion/ Exclusion) criteria[1]	X	X	X										
Disposition: Screening	X												
Disposition: Run-in		X	X										
Disposition: Treatment										X		X	
Pregnancy test (urine)		X							X		X		
Current medication review / adjustment[2]	X												
Dispense rescue medication / Review usage	X	X	X	X	X	X	X	X	X		X		
Contact IRT (IVRS/IWRS)	S	S	S	S	S	S	S	S	S	S	S		
mMRC assessment		X											

Epoch	Screen	Run-In		Treatment									Follow-up
Visit Number	1	101	102*	201*	202	203	204	205	206	207	UV	29[9]	301
Visit	Screening (visit 1)	Run-in (visit 101)	Run-in Visit Part of Day 1	Randomization Visit 201						Study Termination	Treatment Discontin.	Premat. Study Withdrawal	Safety Follow-up
Week	-3 to -2	-2	1	1	1	2	4	8	12	12	—	—	—
Day	-21 to -15	-14	1*	1*	2	15	29	57	85	86	—	—	+30[7]
Urinalysis		X							X		X		
Hematology / biochemistry[5]		X[6]		X[6]					X[6]		X[6]		
Issue and training on patient eDiary		S	S										
Review and upload patient eDiary			S		S	S	S	S	S	S	S		
Physical examination		S								S	S		
Spirometry – Reversibility		X											
Spirometry – Forced Man.				X	X	X	X	X	X	X	X		
Randomization				S									
SDDPI device training		S		S									
Dispense Investigational Drug to patient via IVRS/IWRS				S			S	S					
Administer study drug at the visit				X	X	X	X	X	X				
Record study drug compliance						X	X	X	X		X		
SDDPI Device assessment							S	S	S		S		
ECG		X	X	X		X	X	X	X		X		
Vital signs Systolic / Diastolic BP Radial pulse (sitting)		X	X	X		X	X	X	X		X		
Record height and weight[3]		X							X		X		
Calculate BMI		S											

Epoch	Screen	Run-In		Treatment									Follow-up
Visit Number	1	101	102*	201*	202	203	204	205	206	207	UV	299	301
Visit	Screening (Visit 1)	Run-in (Visit 101)	Run-in Visit Part of Day 1	Randomization Visit 201						Study Termination	Treatment Discontin.	Premat. Study Withdrawal	Safety Follow-up
Week	-3 to -2	-2	1	1	1	2	4	8	12	12	---	---	---
Day	-21 to -15	-14	1*	1*	2	15	29	57	85	86	---	---	+30[7]
Review and record Prior / Concomitant medications	X	X	X		X	X	X	X	X	X	X	X	
SGRQ			X						X		X		
CAT			X						X		X		
BDI /TDI			X						X		X		
SAE recording	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalization occurrence recording[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
COPD exacerbation recording		X	X	X	X	X	X	X	X	X	X	X	X
End of treatment with study drug											X		
Pharmacokinetic sampling[5]							X		X				
Pharmacogenetic sampling[6]				X									
Survival follow-up[7]													X
Study Completion													X

X = assessment to be recorded on clinical data base
S = assessment to be recorded in source documentation only, not to be entered into the eCRF

Visit 299 = Premature study withdrawal (no further study participation or contact)
* Visits 102 and 201 are expected to be conducted on the same visit date. Ensure that the patient questionnaires are completed prior to any other assessment. If rescue medication is administered on Day 1 before the first dose of study treatment, Visit 201 is to be re-scheduled.

[1] Relevant Medical History will be collected on all patients from Visit 1 onward until administration of study medication at Visit 201, and compared to inclusion / exclusion criteria as necessary.
[2] Includes inhaled corticosteroids.
[3] Height will only be collected at Visit 101.
[4] Includes outpatient medical care. Repeat at Visit 201 only if not occurring on the same day as Visit 102.
[5] Pharmacokinetic (PK) samples will be collected in a subset of patients.
[6] Pharmacogenetic sampling will only be collected from consenting patients at Visit 201.
[7] Visit 301 will be conducted 30 days after the patient's last dose of study drug for completed patients (Visit 206), or 30 days after Visit 206 for patients prematurely withdrawn from study treatment, or 30 days after Visit 206 would have taken place for patients who have prematurely terminated their study participation. Non serious AEs that occur within 7 days of the last study dose / visit are to be recorded on the eCRF. SAEs and exacerbations of COPD are to be recorded throughout the entire follow-up period on the appropriate eCRF.
[8] Patients should be fasting at the time of blood sampling for hematology and clinical chemistry. Fasting is defined as patients abstaining from all food and drink for 8 hours prior to a clinic visit, with the exception of water and any medications that are permitted.

Source: Module 5.3.5.1 CSR A2317, Table 6-1, Page 2013, Module 5.3.5.1 CSR A2318, Table 6-1, Page 1907

Patients were encouraged to continue study assessments even after premature discontinuation of study treatment. All data were collected, despite study discontinuation, and the patient was not considered to be withdrawn.

Key Inclusion Criteria

- Male and female adults aged ≥40 years
- Stable, symptomatic COPD with airflow obstruction of level 2 and 3
- According to the current GOLD strategy (GOLD 2011) (i.e. moderate to severe)
- Post-bronchodilator FEV1 ≥ 30% and <80 % of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at Visit 101. Post-bronchodilator referred to 45 min after inhalation of 84 µg ipratropium bromide (or equivalent dose)
- Current or ex-smokers who had a smoking history of at least 10 pack years. An ex-smoker was defined as a subject who had not smoked for ≥ 6 months at screening
- Modified medical research council dyspnea scale (mMRC) grade of at least 2 at Visit 101

Key Exclusion Criteria

- Type I or uncontrolled Type II diabetes.
- History of long QT syndrome or whose QTc measured at Visit 101 (Frederica method) was prolonged (>450 ms for males and females) and confirmed by a central assessor. These patients were not to be re-screened.
- Clinically significant ECG abnormality at Visit 101 or Visit 102. These patients were not to be re-screened
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
- Pregnant or nursing (lactating) women
- Women of child-bearing potential unless they were using effective methods of contraception during dosing of study treatment clinically significant laboratory abnormality at Visit 101.
- Body mass index (BMI) of more than 40 kg/m2
- Clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, New York Health Authority (NYHA) Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the
- Efficacy and safety of the study treatment. paroxysmal (e.g. intermittent) atrial fibrillation were excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months could be considered for inclusion. In such patients, atrial fibrillation had to be present at Visit 101 and baseline Visit 201 visits with a resting ventricular rate < 100/min. At Visit 101 the atrial fibrillation had to be confirmed by central reading.

- Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - anticholinergic agents,
    - long and short acting beta agonists,
    - sympathomimetic amines, or
    - lactose or any of the other excipients of study or rescue medication.
- Narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction severe renal impairment or urinary retention (Benign prostatic hyperplasia patients who were stable on treatment could be considered).
- Patients who had not achieved acceptable spirometry results at screening (Visit 101) in accordance with American Thoracic Society and European Respiratory Society Task Force: Standardization of Lung Function Testing (ATS / ERS) criteria for acceptability and repeatability
- COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to screening (Visit 1). Patients could be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation
- COPD exacerbation between screening (Visit 1) and treatment (Visit 201) were not eligible, but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation
- Respiratory tract infection within 4 weeks prior to screening (Visit 1)
- respiratory tract infection between screening (Visit 1) and treatment (Visit 201) were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection
- Long term oxygen therapy prescribed for >12 hours per day
- History of asthma
- Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years
- Patients with a blood eosinophil count > 600/mm3 during run-in (Visit 101)
- Patients with allergic rhinitis who were using an H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen was permitted)
- Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension)
- Patients with clinically significant bronchiectasis
- Patients with a diagnosis of α-1 anti-trypsin deficiency
- Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active
- Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation
- Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. Participation in a maintenance program was permitted. Note: The supervised pulmonary rehabilitation program as a

maintenance program had to be ongoing for at last 3 months at the time of enrollment into the study (Visit 1)

- Refer to Table 4 for a list of excluded medications
- Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever was longer, or previous participation in the A2318 trial.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action and known adverse events such as worsening narrow angle glaucoma and urinary retention.

Concomitant medication exclusions

Medications that were excluded or had limited use during Studies A2317 and A2318 are summarized in Table 4.

Table 4. Prohibited Medications[1]: Studies A2317 and A2318

Medication	Exclusion Details
Non-selective systemic beta-blocking agents[2]	7 days
Cardiac anti-arrhythmics Class Ia	
Cardiac anti-arrhythmics Class III	
Other drugs with potential to significantly prolong the QT interval	amiodarone 3 months Other drugs with potential to significantly prolong the QT interval 14 days or 5 half-lives, whichever was longer
Tricyclic antidepressants. (Please note that tetracyclics, which were similar in class with regards to drug interaction were also to be excluded)	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants were prohibited	
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	
Monoamine oxidase inhibitors	
Live attenuated vaccine[3]	30 days
Antibiotics (long term maintenance)[4]	
Systematic Mast Cell Stabilizers	7 days
Systemic anticholinergics	
Leukotriene antagonists and leukotriene synthesis inhibitors	
IgE inhibitors (e.g., Xolair)	6 months
Prohibited COPD medications	
Long-acting anticholinergics (LAMA)	7 days
Short acting anticholinergics (SAMA)	8h
Fixed combinations of long-acting β2 agonists and inhaled corticosteroids (LABA/ICS)	48 h (LABA) – Had to be switched to the nearest equivalent dose of inhaled

	corticosteroid monotherapy[5]
Fixed combinations of short-acting β2 agonists and short-acting anticholinergics (SABA/SAMA)	8h
Long-acting β2 agonists (LABA)	48 h (except for indacaterol, where 7 days washout were required)
Short-acting β2 agonists (SABA) (other than study rescue medication)	6h
Intermittent Inhaled corticosteroids[6]	30 days
Oral Phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Systemic corticosteroids	30 days
Intra-muscular depot corticosteroids[7]	3 months
Medications Allowed Under Certain Conditions	
Selective serotonin reuptake inhibitors	Stable dose for at least 30 days prior to the Visit 201 and during the study.
Inhaled corticosteroids (stable long-term regimen)	Stable dose for at least 30 days prior to Visit 201 and during the study.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Visit 201.
H1-antagonists	Stable dose for at least 5 days prior to Visit 201 (except mizolastin or terfenadine).
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to any study visit.

[1]This table was not considered all-inclusive. Medications were to be assessed for adherence to the indication and other inclusion/exclusion criteria.
[2]Selective beta-blockers were permitted.
[3]Inactivated influenza vaccination pneumococcal vaccination or any other inactivated vaccine was also not to be taken within 48 hours of the screening or randomization visit.
[4]Short course of antibiotics were permitted during the study.
[5]The fixed combination was replaced by a free combination of the LABA and the nearest equivalent ICS dose at Visit 2, and the patient instructed when to terminate LABA inhalation to ensure the 48 hour washout period was met.
[6]This related to patients that were on an intermittent dose of ICS prior to the study or newly prescribed ICS as background therapy prior to the study. Nebulized ICS were not permitted during the study. A stable ICS background regimen was permitted.
[7]All ICS, other than depot steroids could be used to treat COPD (exacerbations).

The sponsor did not encourage the cessation of treatment with, and washout of medications, in order to make patients fit the exclusion criteria, unless treatment with these prohibited medications would otherwise have been terminated outside the study.

Source: Module 5.3.5.1, Study A2317 CSR, Table 9-2, p 58-60; Study A2318 CSR, Table 9-2, p 58-60.

COPD exacerbations

At the start of screening (Visit 1) and whenever needed thereafter, all patients will be provided with a salbutamol or albuterol MDI (containing CFC-free propellant; e.g. HFA- 134a), which they will be instructed to use throughout the screening, run-in and treatment epochs of the study (until Visit 207 or UV, respectively) as rescue medication. Nebulized rescue medication is not allowed. Salbutamol / albuterol (100 µg ex-valve / 90 µg ex-actuator) will either be supplied to the investigator sites locally by Novartis, or provided by the study center and reimbursed by Novartis. Patients should be instructed to abstain from taking rescue salbutamol / albuterol

within 6 hours prior to all subsequent study visits (Visits 101 to 207 / UV), and during the entire 12 hour serial measurements at Visits 201 and 206, unless absolutely necessary.

If rescue medication is taken within 6 hours prior to the start of spirometry at Visits 101, 201 or 206, the respective visit should be rescheduled to the next possible day. The investigator must use his / her judgment when deciding how many times a visit for an individual patient should be rescheduled for Visits 101 and 201.

Treatment Groups

Treatment groups are outlined in Table 5.

Table 5. Treatment groups: Studies A2317 and A2318

Substance	GP	Placebo
Pharmaceutical form	capsules for oral inhalation	
Unit strength	12.5 mcg	-
Frequency	one capsule twice daily	
Route of administration	inhalation via single dose dry powder inhaler	

Source: Module 5.3.5.1, Study A2317 CSR, p 4; Study A2318 CSR, p 4.

To maintain blinding, the placebo was designed to match GP; delivered as capsules for oral inhalation, administered as one capsule twice daily inhaled via single-dose dry powder inhaler (SDDPI).

Dose Adjustments

No adjustments to study drug dosage or schedule were permitted, other than temporarily interrupting the study drug during the treatment period of an adverse event (including treatment for a COPD exacerbation), if necessary. Patients were instructed to continue taking study medication during adverse events unless the investigator determined that the continuation of study medication would compromise patient safety.

Patients who experienced a moderate to severe COPD exacerbation were permitted to continue in the study. The duration of time a patient experienced an interruption of study drug was kept to a minimum and any interruption for more than 5 consecutive days was to be discussed with the local Novartis Medical Monitor to review the patient's eligibility to continue in the study. All changes were recorded on the Dosage Administration Record eCRF.

Adverse Events

All adverse events were to be treated appropriately. Treatment could include one or more of the following: no action taken (i.e. further observation only); investigational treatment temporarily interrupted; study drug permanently discontinued; concomitant medication given; non-drug

therapy given. The action taken to treat the adverse event was recorded on the Adverse Event CRF.

Efficacy endpoints

Primary Endpoint

- FEV_1 AUC (0-12h) at Week 12 (measured post-morning dose)

Secondary Endpoints

Further Analysis of Lung Function
- FEV_1 AUC0-4h, AUC4-8h, AUC8-12h, AUC0-12h at Day 1 and Week 12
- Trough and pre-dose FEV_1 and FVC at each visit and each time point
- FEV_1 and FVC at each time-point at each visit
- Peak FEV_1 and FVC during 4 h post morning dose at Day 1 and Week 12

Pharmacological
- Time to onset of action

Patient Reported Outcomes (PRO's)
- TDI focal score at Week 12
- Rescue medication usage
- Symptom scores
- Total SGRQ score and component scores at Week 12
- COPD assessment score (CAT)

Acute Exacerbations
- Number of COPD exacerbations

Vital Signs/Adverse Events
- Adverse events
- Laboratory data
- ECG
- Vital signs

Time to Event Data
- Time to premature treatment discontinuation

Efficacy Endpoint Parameters

Primary Efficacy Parameter

FEV_1 AUC (0-12h) at Week 12

Spirometry measurements at V101were conducted according to and were required to meet ATS/ERS criteria for acceptability and repeatability

Pulmonary function assessments were performed using centralized spirometry. For this purpose, the spirometer was customized and programmed according to the requirements of the study protocol and in accordance with ATS standards (Miller et al 2005), including predicted reference values. In order to reduce the variability of observations, this equipment was used for all measurements during the study. Whenever possible, the same staff member evaluated and coached a given patient at each visit throughout the study. In addition, the spirometer was calibrated every morning before taking any spirometric measurements. Calibration reports were stored as source data.

Secondary Efficacy Parameters

COPD Exacerbations

A descriptive analysis of the number of COPD exacerbations (total, moderate, severe) was performed per treatment group.

In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes was taken as the severity of the collapsed exacerbation.

A COPD exacerbation was defined as:
A worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

OR

A worsening of any 1 major symptom together with an increase in any one of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)

- fever without other cause
- cough
- wheeze

PRO

Total SGRQ score and component scores at Week 12

The derivation of the SGRQ total and component scores and handling of missing data was conducted in accordance with the user guide. The change from baseline in SGRQ total score at Week 12 was analyzed using a linear mixed model (LMM). The model contained treatment, baseline SGRQ total score, smoking status at baseline, and baseline ICS use as fixed effects with center as a random effect.

SGRQ symptoms, activity and impacts components scores were summarized and analyzed using the same mixed model as the SGRQ total score, but with the applicable baseline component score. A decrease of at least 4 in the SGRQ total score is defined as a clinically important improvement. The proportion of patients with a change in SGRQ ≤ -4 was analyzed using logistic regression.

TDI Score

A TDI focal score of ≥1 is defined a clinically important improvement from baseline. The proportion of patients who achieved a clinically important improvement of at least 1 was analyzed using logistic regression. The model contained the same terms as those included in the model used to analyze the TDI focal score.

COPD assessment score (CAT)

The total CAT score was obtained by summing the scores on individual items. Scores of 0 - 10, 11 - 20, 21 - 30 and 31 - 40 represent a mild, moderate, severe or very severe clinical impact of COPD upon the patient. Change from baseline in CAT score at Week 12 was analyzed using the same mixed model as specified for the analysis of SGRQ total score, with baseline SGRQ total score replaced by baseline CAT score.

Compliance Parameters

The days of the first and last use of investigational treatment and any interruption to the regimen were recorded in the eCRF. The Investigator and / or his designee collected the used investigational medication (the SDDPI devices and the blister strips) at Visits 204, 205 and after the evening dose of Visit 206 or at the Study Treatment Discontinuation Visit (UV), respectively. From the capsule count and from information provided by the patient and / or caregiver, study

drug compliance was assessed. Where necessary, the Investigator discussed compliance / documentation issues with the patient.

The time of morning investigational drug administration at Visits 201, 203, 204, 205 and 206 and of the evening administration at Visits 201 and 206 will be collected on the eCRF. The time of dosing is to be taken from the spirometer to avoid deviations in time recordings.

Safety Parameters

The safety analysis was based on the reported AEs, vital signs, physical exam, ECG and review of laboratory data. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Serious adverse events were defined according to the CFR.

Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. An Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) reviewed and approved these studies.

Statistical Plan

Primary Endpoint

The primary objective of the study is to demonstrate the superiority of GP 12.5 mcg BID compared to placebo in terms of FEV_1AUC0-12h at Week 12.

FEV_1 AUC0-12h after 12 weeks treatment was summarized by treatment for the full analysis set (FAS). The treatment contrast of GP versus placebo was evaluated by testing the null hypothesis (H0) versus the alternative hypothesis (Ha) at significance level of 0.05.

ANCOVA analysis for repeated measurements was performed for FEV_1 AUC0-12 at Week 12 without imputation of missing values, with terms of treatment, baseline FEV1 measurements, smoking status at baseline, baseline ICS use, region, visit, treatment * visit interaction and an unstructured error variance-covariance structure assuming normal distribution of the FEV1 data, where visit will be treated as a categorical variable.

The estimated treatment difference between GP 12.5 mcg BID and placebo was displayed along with the associated two-sided 95% confidence interval and p-value (2 sided). Superiority of GP 12.5 mcg BID over placebo was demonstrated if the p-value is less than the 5% significance level and the 95% confidence interval lies entirely to the right of 0 mL.

Secondary Endpoint

FEV_1 AUC0-4h, AUC4-8h, AUC8-12h, AUC0-12h at Day 1 and Week 12
Analyses for these secondary endpoints were conducted using a method similar to that used for the primary endpoint.

FEV_1 and FVC
Trough FEV_1 at Day 1 and Week 12 will be analyzed similarly by using repeated measures ANCOVA method. Similar analysis method is also applied to analyze the treatment effect on FEV_1 measured at each time point at visit 201, 202, 206 and 207. Pre-dose trough FEV_1 at week 12 will be analyzed similarly. For all of treatment contrasts of interest 95% confidence intervals will be provided together with the associated p-value.

The analysis will be repeated for FVC.

Total SGRQ score, CAT score and BDI/TDI

The total score of SGRQ and handling of missing data will be conducted in accordance with the user guide. Total SGRQ score will be analyzed using linear MIXED model. The model will contain treatment, the baseline SGRQ score, smoking status at baseline, and history of inhaled corticosteroid (ICS) use as fixed effects with center nested within region as a random effect. CAT score and BDI/TDI will be analyzed similarly.

Percentage of patients with clinically significant improvement after 12 weeks of treatment in SGRQ (of <=-4 change from baseline) and TDI (of >=1 change from baseline) will be performed using logistic regression model which includes the same terms as used for the analysis of total score.

5.3.2 Studies A2336 and A2337

Study A2336 and A2337 were identically designed trials. The following section outlines the protocol for these studies.

<u>Administrative Information</u>

Study A2336

- **Study title:** A 12-week treatment, multi-center, randomized, double blind, parallel-group, placebo and active controlled study to assess the efficacy, safety, and tolerability of GPI (GP/Ind) in COPD patients with moderate to severe airflow limitation
- **Study dates:** November 28, 2012 – February 28, 2014
- **Study sites:** 150 sites in 8 countries: Canada (21 centers), Spain

(13), Philippines (4), Poland (3), Romania (10), Ukraine (19), United States (76), Vietnam (4).

- **Study report date:** August 13, 2014

Study A2337

- **Study title:** A 12-week treatment, multi-center, randomized, double blind, parallel-group, placebo- and active-controlled study to assess the efficacy, safety, and tolerability of GPI (GP/Ind) in COPD patients with moderate to severe airflow limitation
- **Study dates:** December 3, 2012- February 28, 2014
- **Study sites:** 105 sites were initiated; patients were screened across 104 sites in 9 countries: Colombia (3 centers), Egypt (1), France (4), Guatemala (6), Hungary (11), Panama (3), Slovakia (16), Slovenia (1), United States (59); and 102 sites randomized patients in the study.
- **Study report date:** August 11, 2014

Objectives/Rationale

Primary Objectives

- To demonstrate the superiority of GPI 27.5/12.5 mcg BID compared to monotherapy components, Ind 27.5 mcg BID and GP 12.5 mcg BID, in terms of standardized FEV1 AUC0-12h at Week 12.

Study Design and Conduct

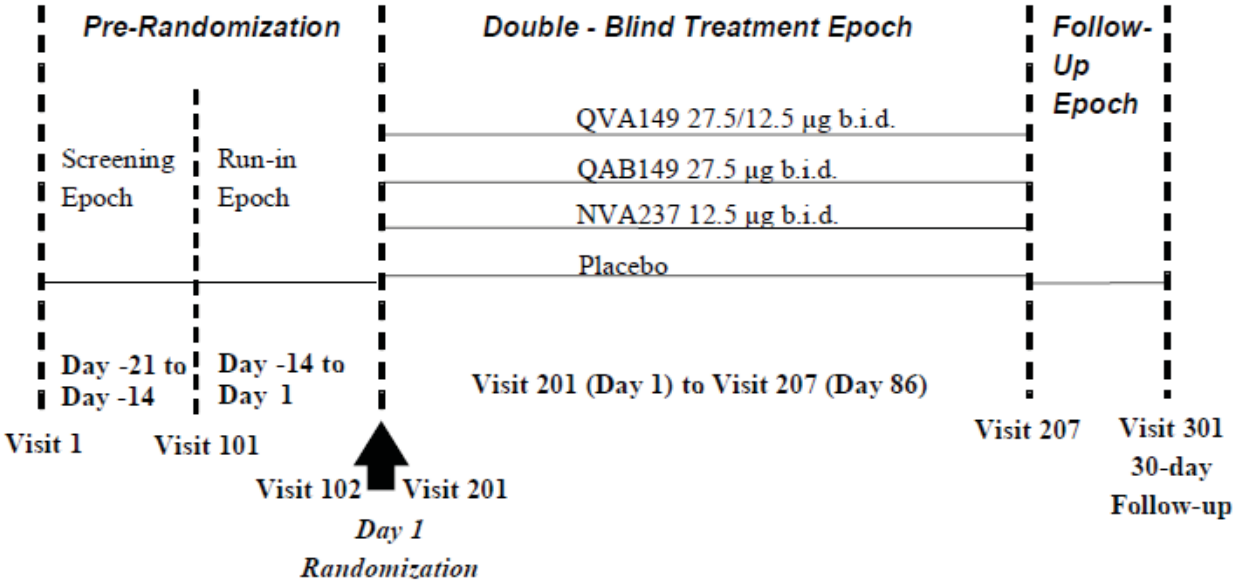
Overview

Study A2336 and A2337 were replicate, 12-week,, phase 3, , multi-center, randomized, double blind, parallel-group, placebo- and active-controlled studies to assess the efficacy, safety, and tolerability of GPI (Ind/GP) in moderate to severe COPD patients. .

The study consisted of a screening epoch, a run-in epoch, a 12 week blinded treatment epoch, and a follow-up epoch of 30 days.

The study design for both studies is depicted in Figure 4.

Figure 4. Study Design Studies A2336 and A2337



QVA149=GPI, QAB149=Ind, NVA237=GP
Source: Module 5.3.5.1 CSR QVA149A2336, Figure 6-1, Page 3335, Module 5.3.5.1 CSR QVA149A2337, Figure 6-1, Page 3206

The schedules of assessments are shown in

APPEARS THIS WAY ON ORIGINAL

Table 6.

Table 6. Schedule of Assessments: Studies A2336 and A2337

APPEARS THIS WAY ON ORIGINAL

Epoch	Screen	Run-in		Treatment									Follow -up
Visit Number	1	101	102*	201*	202	203	204	205	206	207	-	299	301
Visit	Screening	Run-in	End of Run-in	Randomization							TD (Unscheduled)	PSW	Safety Follow-up EOS
Week	-3 to -2	-2				2	4	8	12	12			16
Day	-21 to -14	-14	1	1	2	15	29	57	85	86			30 days after last visit
Obtain informed consent	X												
Contact IRT (IVRS/IWRS)[8]	X	X		X			X	X		X	X	X	
Demographics	X												
Inclusion/Exclusion criteria review	X	X	X										
Relevant Medical History[1]	X	X	X										
CV risk factors history	X												
Pulmonary diseases history	X												
COPD exacerbation history/events	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking History	X												
Smoking status				X					X		X	X	
Pregnancy test (urine)		X							X		X		
Urinalysis		X							X		X		
Hematology/biochemistry		X		X					X		X		
Pharmacokinetic sampling[2]							X		X				
Pharmacogenetic sampling[3]				X									
ECG		X	X	X					X		X		
Physical Exam[8]		X							X		X		
Height		X											
Weight		X							X		X		
BMI calculation		X											
Vital Signs		X	X	X			X		X		X		
Prior and Current medication review/adjustment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X

Epoch	Screen	Run-in		Treatment									Follow -up
Visit Number	1	101	102*	201*	202	203	204	205	206	207	-	299	301
Visit	Screening	Run-in	End of Run-in	Randomization							TD (Unscheduled)	PSW	Safety Follow-up EOS
Week	-3 to -2	-2				2	4	8	12	12			16
Day	-21 to -14	-14	1	1	2	15	29	57	85	86			30 days after last visit
Dispense rescue medication as required /Review use	X	X	X	X	X	X	X	X	X		X		
mMRC		X											
Issue / train patient on eDiary[S]		X		X									
Review and upload patient eDiary[S]			X		X	X	X	X	X	X	X	X	
SGRQ			X						X		X		
CAT			X						X		X		
BDI			X										
TDI									X		X		
Reversibility Spirometry (Centralized)		X											
Spirometry (Centralized)	X[O]			X	X	X	X	X	X	X	X		
Disposition: Screening	X												
Run-in		X**	X										
Treatment										X		X	
Randomization[S]				X									
SDDPI device training[S]		X		X									
SDDPI Device assessment[S]						X	X	X	X		X		
Dispense Study Treatment via IRT[S]				X			X	X					
Administer study treatment at the visit				X	X	X	X	X	X				
Record study treatment compliance						X	X	X	X		X		
End of Study Treatment Epoch										X		X	
Study Completion[S]													X
SAE recording	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X

EOS = End of Study
X = Assessment to be recorded on clinical data base
TD = Study Treatment Discontinuation (permanent treatment discontinuation but continue with limited assessments)
PSW = Premature Study Withdrawal (no further study participation or contact)
[O] Optional practice PFT to be performed in practice mode if necessary.
[S] These assessments are source documentation only and will not be entered into the eCRF.
* Visits 102 and 201 are expected to be conducted on the same visit date. Ensure that the Patient Questionnaires are completed prior to any other assessment. If rescue medication is administered on Day 1 before the first dose of study treatment, Visit 201 is to be re-scheduled.
**If patient is not eligible to continue in Run-in after Visit 101.
[1] Relevant Medical History will be collected on all patients from Visit 1 and until Randomization at Visit 201.
[2] Pharmacokinetic (PK) samples will only be collected in a subset of pts.
[3] Pharmacogenetic samples will only be collected from consenting patients.
[4] Includes inhaled corticosteroids.
[5] Patient will be contacted by a telephone call 30 days after the patient's last dose of study treatment or last visit/observation for safety follow-up.

Source: Module 5.3.5.1 CSR A2336 , Table 6-1, Page 2013, Module 5.3.5.1 CSR A2337, Table 6-1, Page 1907

If premature discontinuation of study treatment occurred for any reason, every effort was made to continue collecting data, especially outcome data, on all patients whether or not they completed treatment. If the patient decided to completely withdraw from the study, all efforts were made to complete and report the observations prior to withdrawal.

Key Inclusion Criteria

- Male and female adults aged ≥40 years.
- Patients with stable COPD according to the current GOLD strategy (GOLD 2011).
- Patients with airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at run-in (Visit 101).
- Post-bronchodilator refers to 1 hour after sequential inhalation of 84 µg ipratropium bromide (or equivalent dose) and 400 µg salbutamol (or 360 µg albuterol). Spacer devices are not permitted during reversibility testing.
- Current or ex-smokers who have a smoking history of at least 10 pack years (e.g.10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker may be defined as a subject who has not smoked for ≥ 6 months at screening.
- Patients with a modified medical research council (mMRC) grade 2 or greater at Visit 101.

Key Exclusion Criteria

- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG (human Chorionic Gonadotropin) laboratory test.
- Women of child-bearing potential, defined as all women physiologically capable of

becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation
  methods) and withdrawal are not acceptable methods of contraception).
  Female sterilization defined as surgical hysterectomy, bilateral oophorectomy, or tubal ligation at least six weeks before taking the study treatment (Single oophorectomy does not meet the definition of female sterilization).
- Male sterilization (at least 6 months prior to screening). For female subjects on the
  study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%),
  for example hormone vaginal ring or transdermal hormone contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

- Patients with Type I or uncontrolled Type II diabetes.
- Patients with a history of long QT syndrome or whose QTc measured at Visit 101 (Fridericia method) is prolonged (>450 ms for males and females) and confirmed by a central assessor. (These patients should not be re-screened)
- Patients who have a clinically significant ECG abnormality at Visit 101 or Visit 102. (These patients should not be re-screened)
- Patients who have a clinically significant laboratory abnormality at Visit 101.
- Patients with a body mass index (BMI) of more than 40 kg/m2.
- Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.

- Patients with paroxysmal (e.g. intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 101 and Visit 102 visits with a resting ventricular rate < 100/min. At Visit 101 the atrial fibrillation must be confirmed by central reading.
- Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - anticholinergic agents
    - long and short acting beta-2 agonists
    - sympathomimetic amines
    - lactose or any of the other excipients of trial medication
- Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
- Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered.
- Patients who have not achieved an acceptable spirometry results at Visit 101 in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability.
- Patients who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to Visit 1. (Patients can be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.)
- Patients who develop a COPD exacerbation between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
- Patients who have had a respiratory tract infection within 4 weeks prior to screening Visit 1 (Re-screen permitted 4 weeks after resolution of the respiratory tract infection)
- Patients who develop a respiratory tract infection between screening and prior to treatment will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
- Patients requiring long term oxygen therapy prescribed for >12 hours per day.
- Patients with any history of asthma.
- Patients with an onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years.
- Patients with a blood eosinophil count > 600/mm3 at Visit 101.
- Patients with allergic rhinitis who use a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose/regimen is permitted).

- Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension).
- Patients with clinically significant bronchiectasis.
- Patients with a diagnosis of α-1 anti-trypsin deficiency.
- Patients with active pulmonary tuberculosis, unless confirmed by imaging to be no longer active.
- Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
- Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study. (Maintenance program is permitted.)
- Patients receiving any medications in the classes listed in Table 7.
- Patients receiving any COPD related medications in the classes specified in Table 7 must undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.
- Patients receiving medications in the classes listed in Table 6 should be excluded unless the medication has been stable for the specified period and the stated conditions have been met.
- Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer or previous participation in the A2337 trial.
- Patients unable to use an electronic patient diary.
- Patients unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication) or comply with the study regimen.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action and known adverse events such as worsening narrow angle glaucoma and urinary retention.

Concomitant medication exclusions

Medications that were excluded or had limited use during Studies A2336 and A2337 are summarized in Table 7.

Table 7. Prohibited Medications[1]: Studies A2336 and A2337

Medication	Exclusion Details
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Non-selective systemic beta-blocking agents[2]	7 days, amiodarone 3 months
Cardiac anti-arrhythmics Class Ia	
Cardiac anti-arrhythmics Class III	

Other drugs with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever was longer
Tricyclic antidepressants. (Please note that tetracyclics, which were similar in class with regards to drug interaction were also to be excluded)	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants were prohibited	
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)	
Monoamine-oxidase inhibitors	
Live attenuated vaccine	30 days
Antibiotics (long term maintenance)[3]	
Systematic Mast Cell Stabilizers	7 days
Systemic anticholinergics	
Leukotriene antagonists and leukotriene synthesis inhibitors	
IgE inhibitors (e.g., Xolair)	6 months
Prohibited COPD medications	
Long-acting anticholinergics (LAMA)	7 days
Short acting anticholinergics (SAMA)	8h
Fixed combinations of long-acting β2 agonists and inhaled corticosteroids (LABA/ICS)	48 h (LABA) – Had to be switched to the nearest equivalent dose of inhaled corticosteroid monotherapy
Fixed combinations of short-acting β2 agonists and short-acting anticholinergics (SABA/SAMA)	8h
Long-acting β2 agonists (LABA)	48 h (except for indacaterol, where 7 days washout were required)
Short-acting β2 agonists (SABA) (other than study rescue medication)	6h
Oral Phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Systemic corticosteroids[4]	30 days
Intra-muscular depot corticosteroids	3 months
Medications Allowed Under Certain Conditions	
Selective serotonin reuptake inhibitors	Stable dose for at least 30 days prior to the Visit 1 and during the study.
Inhaled corticosteroids (stable long-term regimen)	Stable dose for at least 30 days prior to Visit 1 and during the study.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Visit 1.
H1-antagonists	Stable dose for at least 5 days prior to Visit 1 (except mizolastin or terfenadine).
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to any study visit.

[1]This table was not considered all-inclusive. Medications were to be assessed for adherence to the indication and other inclusion/exclusion criteria.
[2]Selective beta-blockers were permitted.

[3]Short course of antibiotics were permitted during the study.
[4] Oral corticosteroids are permitted to treat COPD exacerbation.

The sponsor did not encourage the cessation of treatment with, and washout of medications, in order to make patients fit the exclusion criteria.

Source: Module 5.3.5.1, Study A2336 CSR, Table 5-1, p 3329; Study A2337 CSR, Table 5-1, p 3003.

COPD exacerbations

At the start of Visit 1 (Screening), all patients will be provided with a short acting β2-agonist (salbutamol or albuterol) which they will be instructed to use throughout the study as rescue medication. Nebulized salbutamol or albuterol is not permitted as rescue medication. Salbutamol (100 mcg) or albuterol (90 mcg) will either be supplied to the investigator sites locally by a Novartis designee or provided by the study center and reimbursed by Novartis. During the treatment epoch salbutamol or albuterol should be taken as rescue (when required) purposes only. No other rescue treatment is permitted during the run-in and treatment epochs.

In order to standardize measurements, patients should be instructed to abstain from taking rescue medication (salbutamol or albuterol) within 6 hours of the start of and during each visit where spirometry is being performed unless absolutely necessary.

If rescue medication is taken within 6 hours prior to a spirometry visit, the visit should be rescheduled to the next day, if possible. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled. Visits 202 and 207 must occur the day after Visits 201 and 206, respectively.

In the event that a patient uses a dose of rescue medication after taking study medication at any visit, the visit should continue as planned. In this case the time of rescue medication intake will be captured through the central spirometer.

Treatment Groups

Treatment groups are outlined in Table 8.

Table 8. Treatment groups: Studies A2336 and A2337

Substance	GPI	Ind	GP	Placebo
Pharmaceutical form	capsules for oral inhalation			
Unit strength (mcg)	27.5/12.5	27.5	12.5	-
Frequency	one capsule twice daily			
Route of administration	inhalation via single dose dry powder inhaler			

Source: Module 5.3.5.1: Study A2336 CSR, p 60, Study A2337 CSR, p 57.

To maintain blinding, the placebo was matched to GPI, Ind, and GP.

Dose Adjustments
No adjustments to the study drug dosage or schedule were permitted, other than temporarily interrupting study medication during the treatment period as a result of an AE (including COPD exacerbations), if necessary.

Adverse Events
All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study treatment permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Efficacy Endpoints

Primary Endpoint
- FEV1 AUC0-12h at Week 12

Key Secondary Endpoints
- Total SGRQ score at Week 12

Other Secondary Endpoints

Further Analysis of Lung Function
- Trough FEV_1 at Day 2 and Week 12 (Day 86)
- Pre-dose trough FEV_1
- Trough FVC and pre-dose trough FVC
- FEV_1 and FVC AUC0-4h,AUC4-8h, AUC8-12h, AUC0-6h,AUC6-12h, AUC0-12h at Day 1 and Week 12
- FEV_1 and FVC measurements at each time-point at each visit
- The peak FEV1 (0-4 h)
- The peak FVC (0-4h)
- Numbers and percentages of patients with at least 0.100 L and 0.200 L increase from baseline FEV_1 in AUC0-12h, trough FEV_1, and pre-dose trough at Week 12 (A similar display was also done for FEV_1 at 5min on Day 1)

Pharmacological
- Time to onset of action
- Time to peak action

Patient Reported Outcomes (PRO's)
- TDI focal score at Week 12

- Rescue medication usage
- Symptom scores
- Total SGRQ score and component scores at Week 12
- COPD assessment score (CAT)

Acute Exacerbations
- Number of COPD exacerbations

Vital Signs/Adverse Events
- Adverse events
- Laboratory data
- ECG
- Vital signs

Time to Event Data
- Time to premature treatment discontinuation

Efficacy Endpoint Parameters

Primary Efficacy Parameter

FEV_1 AUC0-12h post morning dose at Week 12

Pulmonary function assessments were performed using centralized spirometry. Spirometers met the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European respiratory Society (ERS) Standardization of Spirometry (Miller et al 2005). The results of the spirometry measurements had to meet ATS/ERS criteria for acceptability and repeatability for the patient to continue in the study. The spirometer was customized and programmed by the eResearchTechnology (ERT, GmbH), according to detailed requirements of the study protocol and in accordance with these standards, including predicted reference values. Extensive training was conducted with site personnel on use of spirometers and pulmonary function assessments. In order to reduce variability of observations and maintain rigorous procedures, the equipment was used for all measurements and as much as possible, the same staff member evaluated and coached a given patient at each visit throughout the study for consistency in patient handling. In addition, the spirometer was calibrated every morning before taking any spirometric measurements. Calibration reports and patient data reports from the spirometer were stored as source data.

Reversibility testing was conducted in the morning and also followed the recommendations of the ATS/ERS Task Force: Standardization of Lung Function testing. Reversibility was

performed to optimize bronchodilation with a short acting beta-2 agonist (SABA) and a short acting muscarinic antagonist (SAMA) to standardize and characterize post bronchodilator FEV1. According to GOLD guidelines, the degree of reversibility of airflow limitation is no longer recommended; due to the limitation in using the data to aid in diagnosis or predict a therapeutic response. Reversibility testing was nevertheless monitored with the same rigor as all the pulmonary function assessments.

Reviewer comment: The use of ATS/ERS Spirometry criteria (2005) is appropriate.

Secondary Efficacy Parameters

COPD Exacerbations

A descriptive analysis of the number of COPD exacerbations (total, moderate, severe) was performed per treatment group.

In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes was taken as the severity of the collapsed exacerbation.

A COPD exacerbation was defined as:
A worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

OR

A worsening of any 1 major symptom together with an increase in any one of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- cough
- wheeze

PRO

Total SGRQ score at Week 12

SGRQ symptoms, activity and impacts components scores were summarized and analyzed using the same mixed model as the SGRQ total score, but with the applicable baseline component score.

The proportion of patients who achieved a clinically important improvement of at least 8 in the SGRQ total score (i.e. a reduction of ≥8 in SGRQ total score) was analyzed using logistic regression model similar to that used for an improvement of at least 4 in the SGRQ total score.

TDI Score

A TDI focal score of ≥1 was defined as a clinically important improvement from baseline. The proportion of patients who achieved a clinically important improvement of at least 1, 2, and 3 units at Week 12 were analyzed using similar model as specified for percentage of patients with clinically significant improvement at Week 12 in SGRQ, with baseline SGRQ being replaced by BDI.

COPD assessment score (CAT)

The total CAT score was obtained by summing the scores on individual items. Change from baseline in CAT score at Week 12 was analyzed using the same mixed model as specified for the analysis of SGRQ total score, with baseline SGRQ total score replaced by baseline CAT score.

Compliance Parameters

The time of study drug administration at each dosing visit was collected on the eCRF. For assessments where spirometry was performed, the time of dosing was taken from the spirometer. While at home, the time of study treatment administration was recorded by the patient in the eDiary. The data from the eDiary was downloaded and reviewed at each visit.

Study treatment compliance was assessed by the investigator and/or center personnel at all visits. The investigator or designee collected the used/unused investigational medication and packaging (unused capsules, blister strips and SDDPIs) from the patient at Visits 203, 204, 205, and 206 (or at TD / PSW visit if applicable). Study treatment compliance was assessed from the capsule count and from information provided by the patient and / or caregiver.

Safety Parameters

The safety analysis was based on the reported AEs, vital signs, physical exam, ECG and review of laboratory data. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Ethics

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Statistical Plan

The primary objective of the study is to demonstrate the superiority of GPI 12.5/27.5 mcg BID compared to its monotherapy components, Ind 27.5 mcg BID and GP 12.5 mcg BID, in terms of FEV_1AUC0-12 at Week 12.

FEV1 AUC0-12h after 12 weeks treatment will be summarized by treatment for the full analysis set (FAS). The treatment contrast of GPI versus Ind or GP was evaluated by testing the null hypothesis (H0) versus the alternative hypothesis (Ha) at significance level of 0.05.

The analyses will be based on the FAS. Treatment differences between GPI 12.5/27.5 mcg BID and Ind 27.5 mcg BID, and between 12.5/27.5 mcg BID and GP 12.5 mcg BID in terms of FEV_1 AUC0-12 at Week 12 will be estimated using ANCOVA for repeated measures,. The model will include terms of treatment, baseline FEV_1 measurements, smoking status at baseline, baseline ICS use, region, baseline FEV1 * visit interaction, and visit, treatment * visit interaction. The within-patient correlation will be modeled using the and an unstructured covariance structure. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Missing values of FEV_1 AUC0-12 at Day 1 and Week 12 will be kept not imputed.

The estimated treatment differences for the previously specified treatment contrasts at Week 12 will be displayed along with the associated 95% confidence interval and p-value. Superiority of GPI to the two monotherapy components will be demonstrated if both p values are less than 0.05.

Secondary Endpoint

FEV_1 AUC0-4h, AUC4-8h, AUC8-12h, AUC0-12h at Day 1 and Week 12

These FEV_1 AUC variables will be analysed similarly to the primary endpoint. The estimated treatment differences for the treatment contrasts will be displayed along with the associated 95% confidence interval and p-value

FEV_1 and FVC

Trough FEV_1 at Day1 and week 12 will be analyzed similarly to the primary endpoint.

Similar analysis method is also applied to analyze the treatment effect on FEV_1 measured at each time point at visit 201, 202, 206 and 207.

Pre-dose trough FEV_1 at week 12 will be analyzed similarly.

For all of treatment contrasts of interest 95% confidence intervals will be provided together with the associated p-value.

The analysis will be repeated for FVC.

Total SGRQ score, CAT score and BDI / TDI
The total score of SGRQ and handling of missing data will be conducted in accordance with the user guide. Total SGRQ score will be analyzed using linear MIXED model. The model will contain treatment, the baseline SGRQ score, smoking status at baseline, and history of inhaled corticosteroid (ICS) use as fixed effects with center nested within region as a random effect.

Percentage of patients with clinically significant improvement after 12 weeks of treatment in SGRQ (of <=-4 change from baseline) will be analyzed using logistic regression model which includes the same terms as used for the analysis of total score.

CAT score will be analyzed using a similar linear MIXED model to that used for the SGRQ. The model will contain treatment, baseline CAT score, smoking status at baseline, and history of inhaled corticosteroid (ICS) use as fixed effects with center nested within region as a random effect.

TDI focal score will be analyzed using a similar linear MIXED model to that used for the SGRQ. The model will contain treatment, the baseline BDI score, smoking status at baseline, and history of inhaled corticosteroid (ICS) use as fixed effects with center nested within region as a random effect. Percentage of patients with clinically significant improvement after 12 weeks of treatment in TDI (of >=1 change from baseline) will be performed using logistic regression model which includes the same terms as used for the analysis of total score.

5.3.3 Study A2319

Administrative Information

- **Study title**: A multi-center, randomized, double-blind, 52-week study to assess the safety of GP compared to Ind in patients with Chronic Obstructive Pulmonary Disease (COPD) who have moderate to severe airflow limitation.
- **Study dates:** October 26, 2012- November 13, 2014
- **Study sites:** 65 centers in the USA
- **Study report date:** December 12, 21014

Objectives/Rationale

Primary Objectives
To evaluate the safety and tolerability of GP 12.5 mcg BID in terms of adverse event (AE) reporting rate in patients with COPD with moderate to severe airflow limitation during 52 weeks of treatment.

Study Design and Conduct

Overview
52-week treatment, multicenter, randomized double-blind, parallel-group design to evaluate the efficacy and safety of GP 12.5 mcg BID in COPD patients with moderate to severe airflow limitation. Study treatment was given in addition to permitted COPD background therapy. The study consisted of 4 epochs; Screening, Run-in, Treatment, and Follow-up. Two interim analyses of safety for review by the DMC were planned when approximately 280 randomized patients had completed 6 months treatment and when approximately 210 randomized patients had completed 52 weeks of treatment, respectively.

The schedule of assessments is summarized in Table 9.

Table 9. Schedule of Assessments A2319

Epoch	Screening	Run-in		Treatment											Follow-up
Visit Number	1	101	102*	201	202	203	204	205	206	207	208	209	Unscheduled	299	301
Visit	Screening	Run-in		Randomization									TD	PSW	Safety Follow-up EOS
Week	-3 to -2	-2	1	1	4	8	12	20	28	36	44	52			
Day	-21	-14	1	1	29	57	85	141	197	253	309	365			
Obtain informed consent	X														
Contact IRT	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Demographics	X														
Inclusion/Exclusion criteria review	X	X	X*												
Relevant Medical History[1]	X	X	X												
Disposition: Screening	X														
Run-in		X	X*												
Treatment												X		X	
Follow-up															X
CV risk factors history	X														
Pulmonary diseases history	X														
COPD exacerbation history	X														
COPD exacerbation events		X	X*	X	X	X	X	X	X	X	X	X	X		
Smoking History	X														
Smoking status				X			X		X	X	X	X	X		
Pregnancy test (urine)		X										X	X		
Urinalysis		X							X			X	X		
Hematology/biochemistry[4]		X					X		X		X	X	X		
ECG		X	X*	X					X			X	X		
Physical Exam		S										S	S		
Height		X													
Weight		X							X			X	X		

Epoch	Screening	Run-in		Treatment											Follow-up
Visit Number	1	101	102*	201	202	203	204	205	206	207	208	209	Unscheduled	299	301
Visit	Screening	Run-in		Randomization									TD	PSW	Safety Follow-up EOS
Week	-3 to -2	-2	1	1	4	8	12	20	28	36	44	52			
Day	-21	-14	1	1	29	57	85	141	197	253	309	365			
BMI calculation		X													
Vital Signs		X		X	X		X		X	X	X	X	X		
Prior and Current medication review/adjustment[2, 5]	X	X	X*	X	X	X	X	X	X	X	X	X	X	X	X
Dispense rescue medication as required /Review use from Week -2	X	X		X	X	X	X	X	X	X	X				
Record Rescue Medication Use		S	S	S	S	S	S	S	S	S	S	S			
Issue / train patient on eDiary		S													
Review and upload patient eDiary			S*		S	S	S	S	S	S	S	S	S		
mMRC		X													
CAT			X				X		X		X	X	X		
Reversibility test/Spirometry		X													
Spirometry (Centralized)				X	X	X	X	X	X	X	X	X	X		
Randomization				S											
SDDPI device training			S	S											
SDDPI Device assessment					S	S	S	S	S	S	S	S			
Dispense Study Drug				S		S	S	S	S	S	S				
Administer study drug at the visit				X	X	X	X	X	X	X	X	X			
Record study drug compliance					X	X	X	X	X	X	X	X	X		
End of study treatment												X	X		
Study Completion															X

Epoch	Screening	Run-in		Treatment											Follow-up
Visit Number	1	101	102*	201	202	203	204	205	206	207	208	209	Unscheduled	299	301
Visit	Screening	Run-in		Randomization									TD	PSW	Safety Follow-up EOS
Week	-3 to -2	-2	1	1	4	8	12	20	28	36	44	52			
Day	-21	-14	1	1	29	57	85	141	197	253	309	365			
Survival follow-up[3, 5]															X
SAE recording[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

X = assessment to be recorded on clinical data base
TD = Treatment discontinuation
PSW = Premature study withdrawal (no further study participation or contact)
S =These assessments are source documentation only and will not be entered into the eCRF
[1]Relevant medical history will be collected on all patients from Visit 1 and until administration of study medication at Visit 201.
[2]Includes inhaled corticosteroids.
[3]Information about a patient's survival will be obtained by a telephone call at Visit301 for all the patients, except those who have refused to have any form of contact.
[4]Fasting requires patients to abstain from all food and drink for 8 hours prior to a clinic visit, with the exception of water and any medications that are permitted.
[5]These assessments will continue to be collected in patients who prematurely discontinue study treatment.
*Assessments on Visit 102 are conducted prior to randomization and are conducted on the same date as Visit 201

Source Module 5.3.5 CSR A2319 page 5662 Table 6-1

Population

The study population was comprised of male or female patients, ≥40 years of age, with a clinical diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2011), with moderate to severe airflow limitation (indicated by a post-bronchodilator FEV1 ≥ 30% and <80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at run-in (Visit 101), and a smoking history of at least 10 pack years. Patients had to have a modified Medical Research Council (mMRC) Dyspnea Scale grade of 2 or greater at run-in Visit 101.

Efficacy Endpoints

- Mean FEV1 at 15 and 45 minutes pre-dose at week 52
- FEV1 and forced vital capacity (FVC) at all post baseline timepoints
- COPD symptoms reported over the 52 week Treatment period
- Daily number of puffs of rescue medication over the 52 week Treatment period
- Time to first moderate or severe COPD exacerbation
- COPD Assessment Test (CAT) score (exploratory)

Safety Endpoints

Safety assessments consisted of collecting all AEs including COPD exacerbations, serious adverse events, clinical labs, vital signs, physical examinations, ECG and pregnancies. An adjudication Committee also evaluated all serious CCV events, atrial fibrillation and atrial flutter events and deaths.

5.3.4 Study A2208

Administrative Information

- **Study title**: A randomized, double-blind, placebo-controlled, 2-period, cross-over study to assess the efficacy and safety of differing doses of GP administered either once daily or twice daily, in patients with moderate to severe chronic obstructive pulmonary disease (COPD)
- **Study dates:** April 23, 2010 – December 28, 2010
- **Study sites:** Belgium (4), Germany (9), Hungary (6), India (5), The Netherlands (7), Poland (4), Romania (1), Spain (3), and USA (11).
- **Study report date:** June 13, 2011

Objectives/Rationale

The primary objective was to evaluate the relationship of incremental doses of GP QD and BID and their effect on trough FEV1 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 GP.

(Trough was defined as the mean of FEV1 measurements at 23 h 15 min and 23 h 45 min post morning dose).

Study Design and Conduct

Overview
This was a multicenter, double-blind, randomized, dose finding trial utilizing an eighttreatment, 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 QD (12.5 mcg QD, 25 mcg QD, 50 mcg QD and 100 mcg QD), and BID (12.5 mcg BID, 25 mcg BID, and 50 mcg BID), and placebo administered over 28 days each.

The schedule of assessments is summarized in Table 10.

Table 10. Schedule of Assessments A2208

	Pre-Screen	SCR/ Run-in	Double blind treatment															
Period			**Period 1**								**Period 2**							
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Day	-15 to -9	-8	1	2	7	8	14	15	28	29	36	37	42	43	49	50	63	64
Obtain informed consent[S]	X																	
Demographics	X																	
Relevant medical history[1]	X	X	X															
COPD exacerbation history	X		X															
Smoking history	X																	
Inclusion/ exclusion criteria[1S]	X	X	X															
Pregnancy test (urine)	X																X	X[2]
Current medication review/adjustment	X																	
Dispense rescue medication[S]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contact IVRS/IWRS[S]	X	X	X							X	X							X[2]
Urinalysis (dipstick)		X							X								X	X[2]
Hematology/ biochemistry		X							X								X	X[2]
Issue and training on patient eDiary[S]		X	X															
Review and upload patient eDiary			X		X		X		X	X	X		X		X		X	X[2]
Physical examination[S]		X															X	X[2]
Reversibility test (anticholinergic)		X																
Spirometry			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]
Randomization[S]			X															
Inhalation device training[S]		X	X								X							
Drug dispensing[S]			X								X							
Administer study drug at the visit[S]			X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Record study drug compliance					X					X			X					X
Device assessment										X								X
Record B_2 agonist use[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X	X						X		X						X	X[2]
Systolic/diastolic BP and radial pulse (sitting)		X	X		X		X		X		X		X		X		X	X[2]
Record height and weight		X																
Review and record prior/concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]
SAE recording (including COPD exacerbations)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]
AE recording (including COPD exacerbations)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]
Study completion																		X[2]

SCR=screening
[S] = these assessments were source documentation only and were not entered into the CRF/database
X = these assessments were recorded in the eCRF/database
[1] Medical history and inclusion/exclusion criteria were collected/assessed on all patients from Visit 1 until administration of study drug at Visit 3
[2] A subset of assessments were performed on patients who prematurely discontinued from the study: single assessment ECG, blood pressure, single maneuver spirometry, physical examination, urinalysis, hematology/biochemistry, pregnancy test, capsules taken, device assessment, any AEs/exacerbations, any changes to concomitant medications and call IVRS/IWRS
[3] Beta 2 agonist use prior to the clinic visit was recorded in the central spirometer and not in the eCRF

Source Module 5.3.5 CSR A2208 page 78 Table 9-7

Population

The main inclusion criteria were: male or female adults ≥40 years of age, 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 FEV1 ≥30% and < 80% of the predicted normal, and post-bronchodilator FEV1/FVC < 0.7 at Visit 2 :Post refers to 45 mins after inhalation of 84 µg ipratropium bromide). Symptomatic patients, according to daily electronic diary data between Visit 2 and Visit 3, with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3.

Main exclusion criteria were: pregnant women or nursing mothers, and women of child-bearing potential; a history of long QT syndrome or whose QTc measured at Visit 2 was prolonged (>450 ms); a clinically relevant laboratory abnormality or a clinically significant condition including unstable ischemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia; history of malignancy of any organ system (including lung cancer) within the past 5 years, with the exception of localized basal cell carcinoma of the skin; narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention, uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state; any condition which might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study. Patients were also excluded that had either a history of asthma, were atopic, were receiving any prohibited medications unless an appropriate washout period was observed, required long term oxygen therapy (> 15 h a day) on a daily basis for chronic hypoxemia, had a respiratory tract infection within 4 weeks prior to Visit 1, had a COPD exacerbation that required treatment with antibiotics or oral glucocorticosteroids or hospitalization in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 3, had allergic rhinitis that was not on a stable dose of either a H1 antagonist or intra-nasal corticosteroids, were participating in the active phase of a pulmonary rehabilitation programme, had a known history and diagnosis of alpha-1 anti-trypsin deficiency, a lung lobectomy or lung volume reduction or lung transplantation, concomitant pulmonary disease, history of hypersensitivity to any of the study drugs or to drugs of a similar class or any component thereof (anticholinergic agents, long and short acting beta-2 agonists, sympathomimetic amines), use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of Visit 1,

whichever was longer, patients unable to use a dry powder inhaler (SDDPI) device or pMDI (rescue medication).

Efficacy Endpoints

The main objective of this study was to characterize the GP dose versus trough FEV_1 relationship for QD and BID regimens. Non-linear mixed effects modeling was used for this purpose. The primary analysis variable was trough FEV_1 (calculated as the average of the 23h 15min and 23h 45min measurements). A key secondary modeling outcome, the maximum difference in mean response between BID and QD regimens, was derived from the primary analysis of trough FEV_1. Important secondary analyses were based on standardized FEV_1 AUC 0-24h. The AUC values were determined for a common set of time points on Days 1, 14 and 28. FEV_1 AUC 0-24h was also derived using all measurements collected on Day 28.

Other secondary endpoints included FEV_1 AUC 0-4h, FEV_1 AUC 0-8h, FEV_1 AUC 0-12h and FEV_1 AUC 12- 24h, standardized using the same process described for FEV_1 AUC0-24h (see 'Important secondary analyses' below). Additionally, FEV_1 at 12h, peak FEV_1, FVC and weekly rescue medication use were included in the other secondary endpoint analyses.

Safety Endpoints

Safety assessments consisted of collecting all AEs, SAEs, with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of ECGs performed at a central laboratory, and hematology, blood chemistry and urinalysis via dipstick performed at a central laboratory. There were regular assessments of vital signs and physical condition.

6 Review of Efficacy

Efficacy Summary

To support the proposed indication, the Applicant submitted data from one dose ranging/regimen study (A2208) and two replicate 12-week confirmatory trials (A2317 and A2318). Study A2208 was a 28-day randomized, double blind, placebo-controlled, crossover, dose ranging study of glycopyrrolate (GP) in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Studies A2317 and A2318 were replicate, phase 3, 12-week, randomized, double-blind, placebo-controlled, multicenter studies to assess the efficacy, safety and tolerability of GP 12.5 mcg BID versus placebo in patients with moderate to severe COPD. Additional supportive efficacy was provided by studies A2336 and A2337 which were conducted as part of the combination GP/Indacaterol development program and included single-ingredient GP treatment arms as part of the typical factorial design.

The phase 3 studies enrolled adult males and females aged 40 years and older with a clinical diagnosis of stable, moderate to severe COPD (airflow obstruction of level 2 and level 3, GOLD 2011), a smoking history of at least 10 pack years, a postbronchodilator FEV1 ≥ 30% and < 80% of the predicted normal, and a post-bronchodilator FEV1/FVC < 0.70 at screening. Patients were excluded at screening if there was any history of asthma, lower levels of persistent airflow limitation (less than 30% predicted normal FEV1), or an onset of respiratory symptoms before 40 years of age. Studies (A2317 and A2318) enrolled a total of 873 COPD patients; 438 to GP 12.5 mcg BID and 435 to placebo.

Baseline demographics were fairly balanced across treatment groups is generally representative of the population in whom COPD is known to occur. The median age for the 2 studies ranged from 63-64 years, with a majority being white (86-92%) males (56-60%), 40-64 years of age (52-58%). These studies were conducted fully in the United States. Of the study population, 5 to 13% were black patients.

The primary endpoint in the replicate phase 3 studies (A2317 and A2318) was FEV1 AUC(0-12h) at Week 12. The LS mean treatment difference for change from baseline in FEV1 AUC(0-12h) was statistically significant for GP versus placebo at 12 weeks (0.139 L and 0.123 L, p<0.001, respectively) for both studies (A2317 and A2318).

The secondary endpoint SGRQ, when analyzed via a responder analysis, where a response was defined as those patients who achieved and MCID ≥-4, GP did not demonstrate a statistically significant effect vs. placebo (OR: 1.43, 95% CI [0.95, 2.15]) in study A2317. In study A2318 the responder analysis, showed that GP demonstrated a statistically significant effect vs. placebo (OR: 1.78, 95% CI [1.17, 2.71]).

Overall, the efficacy of GP for the treatment of COPD has been demonstrated. Two replicate phase 3 studies showed a statistically significant difference in the primary efficacy endpoint of FEV1 AUC(0-12h).

6.1 Indication

The proposed indication for glycopyrrolate is for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

6.1.1 Methods

The focus of this efficacy review is derived from Studies A2208, A2317, A2318, A2336, and A2337. Study A2208 was a 28-day randomized, double blind, placebo-controlled cross-over dose ranging study. Studies A2317 and 2318 were replicate, multicenter, 12-week, randomized, double-blind, placebo-controlled, studies of GP 12.5 mcg BID compared to placebo in patients with moderate-to-severe COPD. Studies A2336 and A2337 were conducted in support of the

GP/Ind combination product, but include GP monotherapy and placebo arms, and provide support to the results seen in A2317 and A2318, and will therefore be included in this review. For full details regarding the Agency's statistical analyses of the Applicant's results, refer to the Biometrics Review by Dr. Kiya Hamilton.

6.1.2 Demographics

Studies A2317 and A2318

The demographics for the study population in studies A2317 and A2318 are displayed in Table 11.

Table 11. Demographics- A2317 and A2318

	Study A2317		Study A2318	
	GP 12.5 mcg BID N=222	**Placebo N=219**	**GP 12.5 mcg BID N=216**	**Placebo N=216**
Female n (%)	98 (44.1)	87 (39.7)	88 (40.7)	90 (41.7)
Age Categories, n (%)				
40-64 years	129 (58.1)	127 (58.0)	114 (52.8)	112 (51.9)
65-74 years	71 (32.0)	80 (36.5)	75 (34.7)	80 (37.0)
≥75 years	22 (9.9)	12 (5.5)	27 (12.5)	24 (11.1)
Mean age (SD)	62.7 (8.4)	62.1 (8.3)	63.9 (8.6)	64.2 (8.4)
Race, n (%)				
White	205 (92.3)	193 (88.1)	190 (88.0)	185 (85.6)
Asian	2 (0.9)	2 (0.9)	1 (0.5)	1 (0.5)
Black	12 (5.4)	19 (8.7)	19 (8.8)	27 (12.5)
Native American	0	1 (0.5)	2 (0.9)	3 (1.4)
Pacific Islander	0	0	1 (0.5)	0
Other	3 (1.4)	4 (1.8)	3 (1.4)	0
Mean BMI kg/m2 (SD)	28.2 (5.2)	27.7 (5.6)	28.4 (5.4)	28.2 (5.4)
US site (%)	100%	100%	100%	100%

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-3, page 33, Table 3-4, page 34

Baseline demographics were fairly balanced across treatment groups. The median age for the 2 studies ranged from 63-64 years, with a majority being white (86-92%) males (56-60%), 40-64 years of age (52-58%). These studies were conducted fully in the United States. Of the study population, 5 to 13% were black patients.

Studies A2336 and A2337

The demographics for the study population in studies A2336 and A2337 are displayed in Table 12.

Table 12. Demographics- A2336 and A2337

	Study A2336				Study A2337			
	GPI 12.5/27.5 mcg BID N=260	**Ind 27.5 mcg BID N=260**	**GP 12.5 mcg BID N=261**	**Placebo N=261**	**GPI 12.5/27.5 mcg BID N=250**	**Ind 27.5 mcg BID N=251**	**GP 12.5 mcg BID N=251**	**Placebo N=249**
Age Categories, n (%)								
40-64 years	132 (50.8)	143 (55.0)	140 (53.6)	143 (54.8)	143 (57.2)	130 (51.8)	144 (57.4)	148 (59.4)
65-74 years	93 (35.8)	91 (35.0)	89 (34.1)	90 (34.5)	84 (33.6)	94 (37.5)	84 (33.5)	81 (32.5)
≥75 years	35 (13.5)	26 (10.0)	32 (12.3)	28 (10.7)	23 (9.2)	27 (10.8)	23 (9.2)	20 (8.0)
Mean age (SD)	63.9 (8.76)	63.7 (8.07)	63.7 (8.35)	63.7 (8.19)	62.8 (8.46)	63.7 (8.58)	63.1 (8.53)	62.5 (8.07)
Female n (%)	90 (34.6)	74 (28.5)	78 (29.9)	92 (35.2)	96 (38.4)	101 (40.2)	107 (42.6)	111 (44.6)
Race, n (%)								
White	241 (92.7)	239 (91.9)	230 (88.1)	244 (93.5)	230 (92.0)	224 (89.2)	222 (88.4)	227 (91.2)
Asian	8 (3.1)	10 (3.8)	13 (5.0)	8 (3.1)	0	1 (0.4)	0	0
Black	10 (3.8)	8 (3.1)	15 (5.7)	8 (3.1)	7 (2.8)	11 (4.4)	9 (3.6)	11 (4.4)
Native American	0	0	1 (0.4)	1 (0.4)	12 (4.8)	15 (6.0)	19 (7.6)	10 (4.0)
Other	1 (0.4)	2 (0.8)	2 (0.8)	0	1 (0.4)	0	1 (0.4)	1 (0.4)
Mean BMI kg/m2 (SD)	27.2 (4.9)	27.6 (5.2)	27.7 (5.2)	27.2 (5.2)	27.2 (4.9)	27.7 (5.2)	27.6 (5.7)	26.7 (5.6)
US site (%)	48.9%				59.6%			

Source: NDA 207930 Module 2.7.3, Summary of Clinical Efficacy, Table 3-3, page 34, Table 3-4, page 36

Baseline demographics were fairly balanced across treatment groups. The mean age for the 2 studies ranged from 63-64 years, with a majority being white (88-94%) males (55-62%), 40-64 years of age (51-59%). Of the study population, 3 to 6% were black patients.

Studies A2317 and A2318

The baseline disease characteristics for the study population in studies A2317 and A2318 are displayed in Table 13.

Table 13. Baseline COPD Characteristics- A2317 and A2318

	Study A2317		Study A2318	
	GP 12.5 mcg BID N=222	**Placebo N=219**	**GP 12.5 mcg BID N=216**	**Placebo N=216**
Mean FEV_1 (L) pre-bronchodilator (SD)	1.3 (0.5)	1.3 (0.5)	1.3 (0.4)	1.3 (0.5)
Number of COPD exacerbations in the previous year, n (%)				
0	174 (78.4)	165 (75.3)	176 (81.5)	161 (74.5)
1	42 (18.9)	41 (18.7)	30 (13.9)	40 (18.5)
≥2	6 (2.7)	13 (5.9)	10 (4.6)	15 (6.9)
Duration of COPD (years) (median)	5.4	4.9	5.2	5.8
+ ICS use at baseline, n (%)	54 (24.3)	62 (28.3)	68 (31.5)	70 (32.4)
Smoking history, n (%)				
Ex-smoker	85 (38.3)	87 (39.7)	101 (46.8)	101 (46.8)
Current smoker	137 (61.7)	132 (60.3)	115 (53.2)	115 (53.2)
Severity of COPD, n (%)				
Mild (GOLD 1)	0	0	0	1 (0.5)
Moderate (GOLD 2)	138 (62.2)	144 (65.8)	139 (64.4)	125 (57.9)
Severe (GOLD 3)	83 (37.4)	73 (33.3)	73 (33.8)	85 (39.4)
Very Severe (GOLD 4)	0	0	0	0
Missing	1 (0.5)	2 (0.9)	1 (0.5)	1 (0.5)

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-5, page 35, Table 3-6, page 36, Table 3-7. page 37, Table 3-8, page 38, Table 3-9, page 39, Table 3-10, page 40

The COPD characteristics were fairly balanced across treatment groups and typical of the chosen population. A majority of the patients had zero exacerbations in the previous year and were classified as having moderate (GOLD 2) COPD as seen Table 13.

Studies A2336 and A2337

The baseline disease characteristics for the study population in studies A2317 and A2318 are displayed in Table 14.

Table 14. Baseline COPD Characteristics- A2336 and A2337

	Study A2336				Study A2337			
	GPI 12.5/27.5 mcg BID N=260	**Ind 27.5 mcg BID N=260**	**GP 12.5 mcg BID N=261**	**Placebo N=261**	**GPI 12.5/27.5 mcg BID N=250**	**Ind 27.5 mcg BID N=251**	**GP 12.5 mcg BID N=251**	**Placebo N=249**
Mean FEV_1 (L) pre-bronchodilator (SD)	1.3 (0.4)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.5)
Number of COPD exacerbations in the previous year, n (%)								
0	173 (66.5)	173 (66.5)	170 (65.1)	166 (63.6)	177 (70.8)	185 (73.7)	179 (71.3)	185 (74.3)
1	73 (28.1)	65 (25.0)	72 (27.6)	72 (27.6)	59 (23.6)	53 (21.1)	52 (20.7)	49 (19.7)
≥2	14 (5.4)	22 (8.5)	19 (7.3)	23 (8.8)	14 (5.6)	13 (5.2)	20 (8.0)	15 (6.0)
Duration of COPD (years) (median)	5.5	5.6	5.7	5.6	6.4	5.7	5.7	5.8
+ ICS use at baseline, n (%)	124 (47.7)	140 (53.8)	119 (45.6)	130 (49.8)	109 (43.6)	110 (43.8)	100 (39.8)	101 (40.6)
Smoking history, n (%)								
Ex-smoker	134 (51.5)	130 (50.0)	130 (49.8)	132 (50.6)	118 (47.2)	115 (45.8)	114 (45.4)	115 (46.2)
Current smoker	126 (48.5)	130 (50.0)	131 (50.2)	129 (49.4)	132 (52.8)	136 (54.2)	137 (54.6)	134 (53.8)
Severity of COPD (Gold 2011) - Airflow limitation, n (%)								
Moderate (GOLD 2)	162 (62.3)	153 (58.8)	155 (59.4)	164 (62.8)	153 (61.2)	151 (60.2)	160 (63.7)	142 (57.0)
Severe (GOLD 3)	97 (37.3)	105 (40.4)	105 (40.2)	95 (36.4)	95 (38.0)	99 (39.4)	87 (34.7)	105 (42.2)
Very Severe (GOLD 4)	0	0	1 (0.4)	0	0	0	0	0

COPD= chronic obstructive pulmonary disease, ICS= inhaled corticosteroid, SD= standard deviation, GOLD= Global Initiative for Chronic Obstructive Lung Disease, GOLD 2011 was used
One patient was randomized twice and is counted twice in the randomized set
Duration of COPD was calculated from the date first diagnosed with COPD recorded on the eCRF until Visit 1
Smoking status at baseline Visit 201 is shown
% of predicted FEV1 was obtained as a percentage of FEV1 relative to the predicted normal value

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-5, page 37, Table 3-6, page 38, Table 3-7. page 39, Table 3-8, page 39, Table 3-9, page 40, Table 3-10, page 41

The COPD characteristics were fairly balanced across treatment groups and typical of the chosen population. A majority of the patients had zero exacerbations in the previous year and were classified as having moderate (GOLD 2) COPD.

6.1.3 Subject Disposition

Studies A2317 and A2318

Subject disposition is described in Table 15.

Table 15. Disposition- A2317 and A2318

	Study A2317		Study A2318	
Disposition Reason	**GP 12.5 mcg BID N=222 n (%)**	**Placebo N=219 n (%)**	**GP 12.5 mcg BID N=216 n (%)**	**Placebo N=216 n (%)**
Randomized	222	219	216	216
Completed planned treatment phase	215 (96.8)	208 (95.0)	209 (96.8)	205 (94.9)
Discontinued planned treatment phase	7 (3.2)	11 (5.0)	7 (3.2)	11 (5.1)
Primary reason for discontinuation of planned treatment phase				
Subject/guardian decision	5 (2.3)	6 (2.7)	7 (3.2)	9 (4.2)
Lost to follow up	1 (0.5)	0	0	2 (0.9)
Non-compliance with study treatment	1 (0.5)	1 (0.5)	-	-
Adverse event	0	2 (0.9)	-	-
Death	0	1 (0.5)	-	-
Physician decision	0	1 (0.5)	-	-

Patients could discontinue from study treatment but continue participating in the study, therefore "completed planned treatment phase" row includes all patients who completed the treatment phase whether on study treatment or not. The primary reason for discontinuation as given by the investigator on the Treatment Phase Disposition/ Premature Study Withdrawal eCRF was summarized. Percentages are based on the number of randomized patients.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-1, page 31, Table 3-2, page 32

Most patients completed the planned treatment phase (95-97%). The number of patients who discontinued early was also fairly balanced, with slightly higher premature discontinuations in the placebo group. The most common reason for premature discontinuation was subject/guardian decision.

Studies A2336 and A2337

Subject disposition is described in Table 16.

Table 16. Disposition- A2336 and A2337

	Study A2336				Study A2337			
Disposition Reason	**GPI 12.5/27.5 mcg BID N=260**	**Ind 27.5 mcg BID N=260**	**GP 12.5 mcg BID N=261**	**Placebo N=261**	**GPI 12.5/27.5 mcg BID N=250**	**Ind 27.5 mcg BID N=251**	**GP 12.5 mcg BID N=251**	**Placebo N=249**
Randomized	260	260	261	261	250	251	251	249
Completed planned treatment epoch	255 (98.1)	251 (96.5)	258 (98.9)	246 (94.3)	244 (97.6)	241 (96.0)	245 (97.6)	236 (94.8)
Discontinued planned treatment epoch	5 (1.9)	9 (3.5)	3 (1.1)	15 (5.7)	6 (2.4)	10 (4.0)	6 (2.4)	13 (5.2)
Primary reason for discontinuation of planned treatment phase								
Subject/guardian decision	4 (1.5)	4 (1.5)	2 (0.8)	11 (4.2)	3 (1.2)	9 (3.6)	3 (1.2)	9 (3.6)
Physician decision	0	1 (0.4)	0	2 (0.8)	2 (0.8)	0	0	1 (0.4)
Protocol deviation	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)	0	1 (0.4)	0
Death	0	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.4)	0	0
Lost to follow up	0	2 (0.8)	0	0	0	0	2 (0.8)	1 (0.4)
Technical problems	0	0	0	0	0	0	0	2 (0.8)

Patients could discontinue from study treatment but continue participating in the study, therefore 'completed planned treatment epoch' row includes all patients who completed the treatment epoch whether or not they completed study treatment.
The primary reason for planned Treatment Epoch discontinuation was summarized as given by the investigator on the Treatment Epoch Disposition/Premature Study Withdrawal eCRF.
Reason for discontinuation by withdrawal of consent is represented by 'Subject/ guardian decision'
Percentages are based on the number of randomized patients.
One patient was randomized twice and is counted multiple times as screened and twice in the randomized set.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-1, page 33, Table 3-2, page 34

Most patients completed the planned treatment phase (94-99%). The number of patients who discontinued early was also fairly balanced, with slightly higher premature discontinuations in the placebo group. The most common reason for premature discontinuation was subject/guardian decision.

Study A2319

Table 17. Subject Disposition A2319

Disposition Reason	GP 12.5 mcg BID n (%)	Ind 75 mcg QD n (%)	Total n (%)
Screened	-	-	1296
Treated but not randomized#	0	1	1
Randomized	254	257	511
Completed planned treatment phase	207 (81.5)	210 (81.7)	417 (81.6)
Discontinued planned treatment phase	47 (18.5)	47 (18.3)	94 (18.4)
Primary reason for discontinuation of planned treatment phase			
Subject/guardian decision	31 (12.2)	35 (13.6)	66 (12.9)
Lost to follow up	10 (3.9)	7 (2.7)	17 (3.3)
Death	4 (1.6)*	2 (0.8)*	6 (1.2)*
Physician decision	1 (0.4)	0	1 (0.2)
Protocol deviation	1 (0.4)	0	1 (0.2)
Study terminated by sponsor@	0	3 (1.2)	3 (0.6)

Number of "randomized" includes five patients who were excluded from the FAS and safety set because of multiple enrollment with overlapping treatment epochs.
Patients can discontinue from study treatment but continue participating in the study, therefore "completed planned treatment phase" row includes all patients who have completed the treatment phase whether on study treatment or not.
The primary reason for discontinuation as given by the investigator on the Treatment Phase.
Disposition/Premature Study Withdrawal eCRF is summarized.
Percentages are based on the number of randomized patients.
* 2 deaths in the GP 12.5 mcg BID group and 1 death in the Ind 75 mcg QD group occurred more than 30 days after last dose of study medication.
#One patient from site 5044 was provided treatment in error without randomization.
@ Site 5056 was prematurely closed due to critical GCP non-compliance issues.

Source: Module 5.3.5 Study A2319 CSR, p 4

Most patients completed the planned treatment phase of the 52 week study (~82%). The number of patients who discontinued early was also fairly balanced.

6.1.4 Analysis of Primary Endpoint(s)

Studies A2317 and A2318

The primary objective of the studies was to demonstrate the superiority of GP compared to placebo in terms of change from baseline in FEV_1 AUC0-12h at Week 12.

Table 18. FEV_1 (L) AUC(0-12h) at Week 12 (FAS) – A2317 and A2318

		Treatment Difference		
Study Treatment	**CFB in FEV_1 AUC LS Mean (SE)**	***LS Mean (SE)**	**95% CI**	**p-value**
Study A2317				
GP 12.5 mcg BID N=222	0.125 (0.0162)	0.139 (0.0225)	(0.095, 0.184)	<0.001
Placebo N=216	-0.014 (0.0165)			
Study A2318				
GP 12.5 mcg BID N=215	0.115 (0.0153)	0.123 (0.0213)	(0.081, 0.165)	<0.001
Placebo N=213	-0.008 (0.0153)			

CFB: change from baseline, LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval
*MMRM: (mixed model for repeated measures) change from baseline in FEV1 AUC = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit (Days 1 and 85) + treatment * visit interaction + baseline FEV1 * visit interaction.

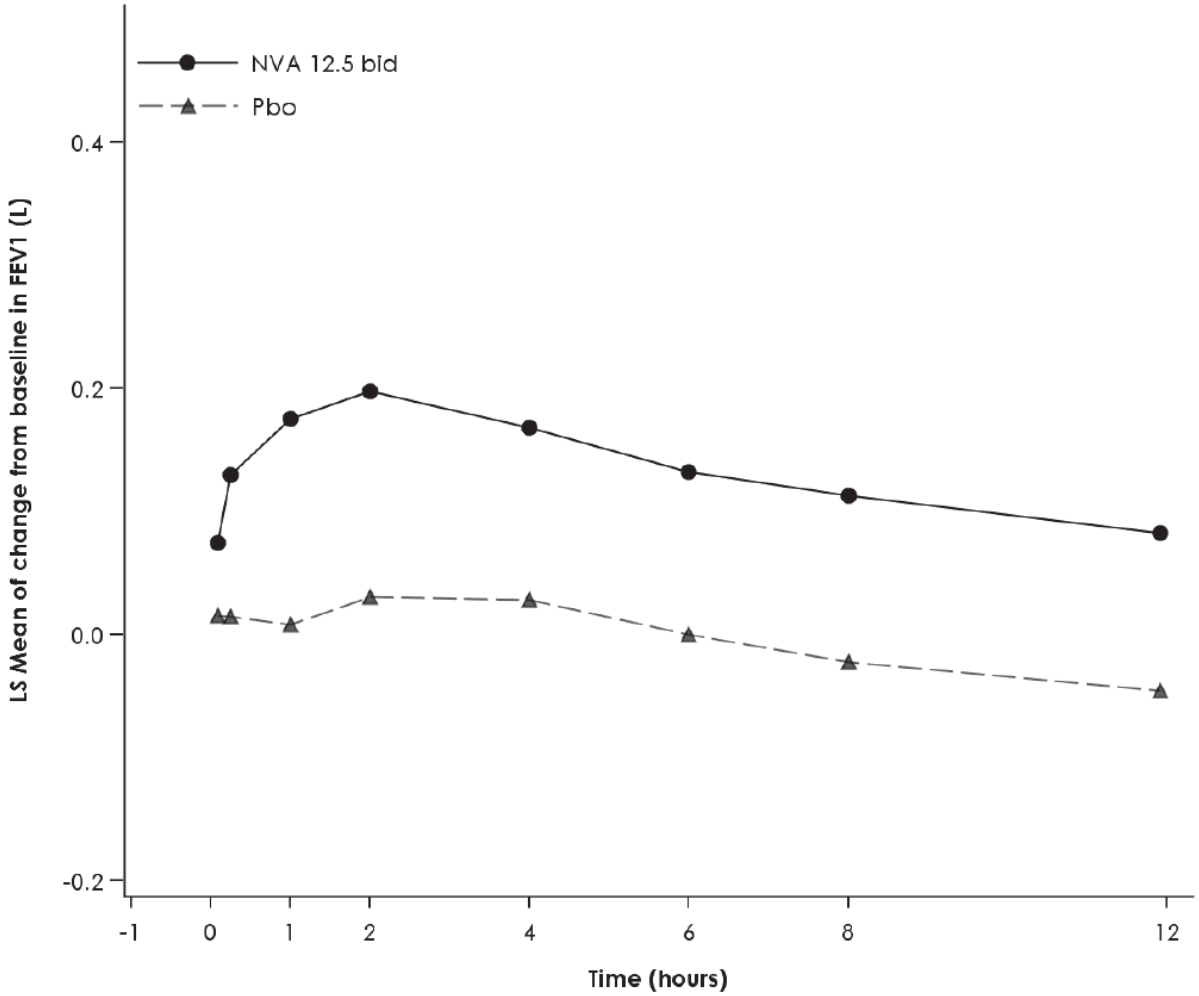
Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-20, page 55

As described in Table 18, the LS mean treatment difference for change from baseline in FEV_1 AUC(0-12h) was statistically significant for GP versus placebo at 12 weeks (0.139 L and 0.123 L, p<0.001, respectively) for both studies (A2317 and A2318).

Serial spirometric evaluations throughout the 12-hour dosing interval were performed in all subjects on Days 1 and 85 (Week 12), and are displayed in Figure 5 and

Figure 6 for Study A2317 and in Figure 7 and Figure 8 for Study A2318, respectively. These FEV_1 profiles at the beginning and end of the treatment period provide support for the duration of treatment effect over the entire dosing interval.

Figure 5. Change from baseline in FEV_1 (L) from 5 min up to 11 h 55 min post-dose on Day 1 (FAS) – Study A2317

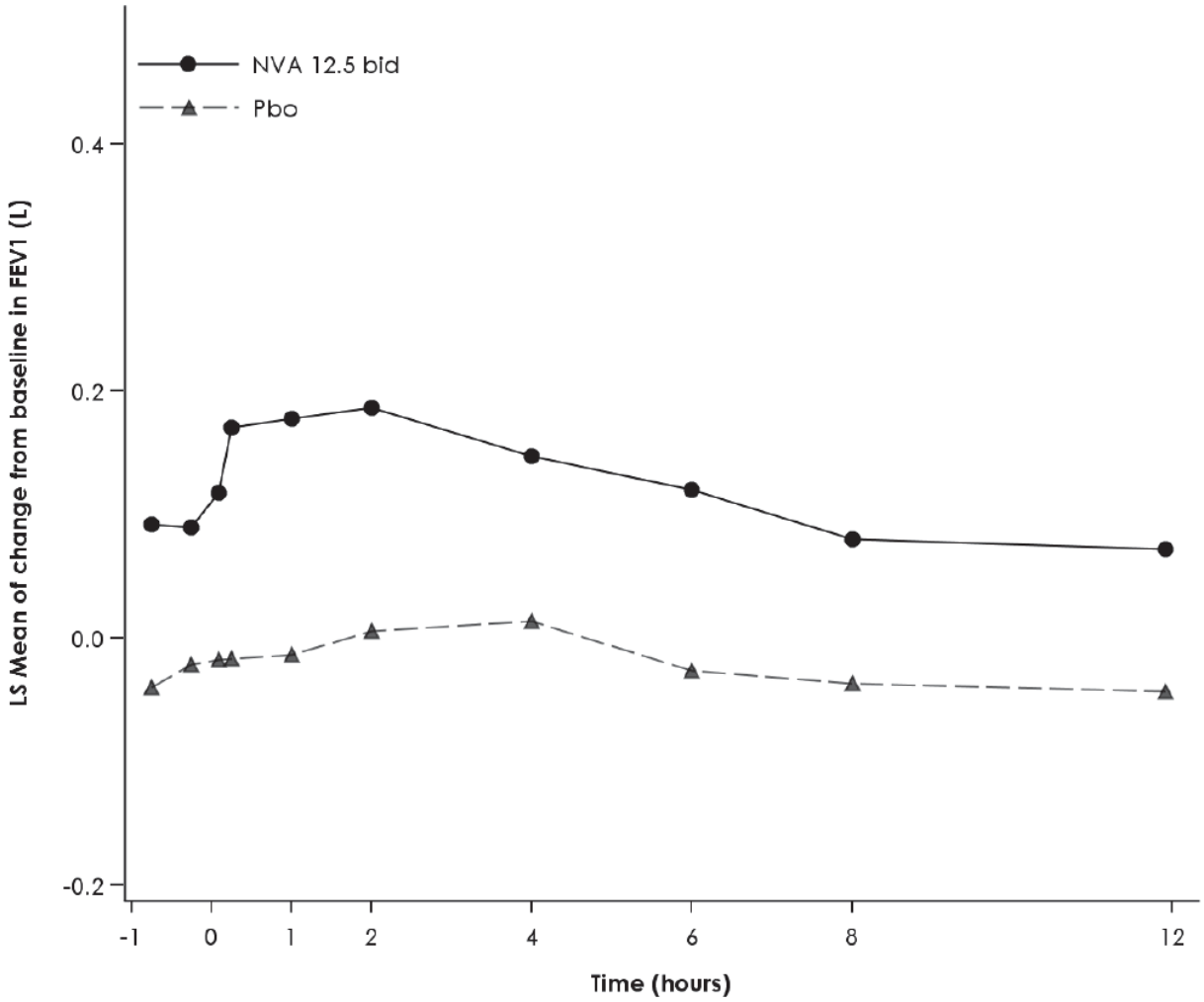


NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: Change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction. Separate MMRM were performed for each timepoint using visit as repeated variable.
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-1, Page 56

Figure 6. Change from baseline in FEV_1 (L) from -45 min to 11 h 55 min on Day 85 (FAS) – Study A2317

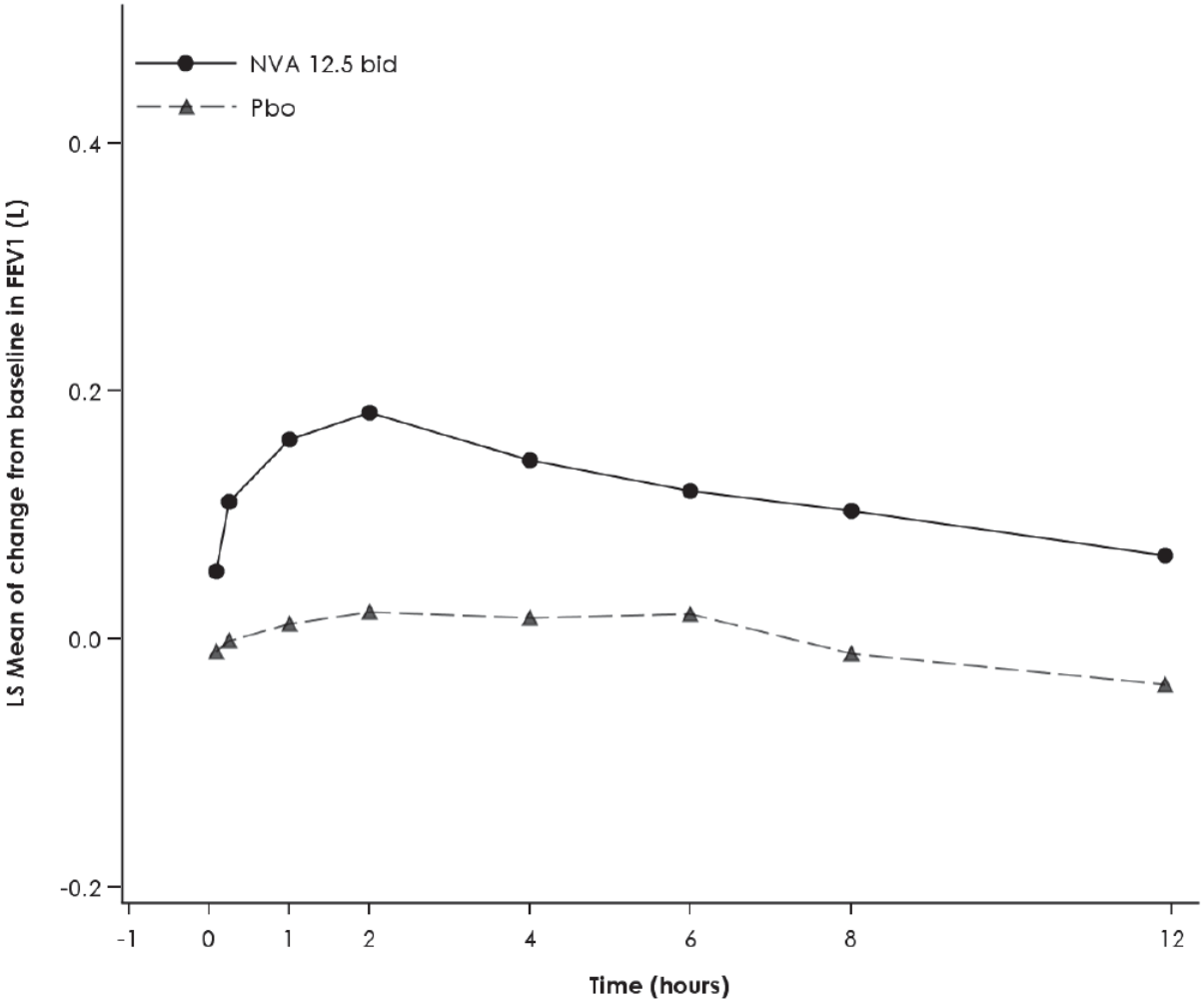


NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: Change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Separate MMRM were performed for each timepoint using visit as repeated variable.
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-2, page 57

Figure 7. Change from baseline in FEV_1 (L) from 5 min up to 11 h 55 min post-dose on Day 1 (FAS) – Study A2318

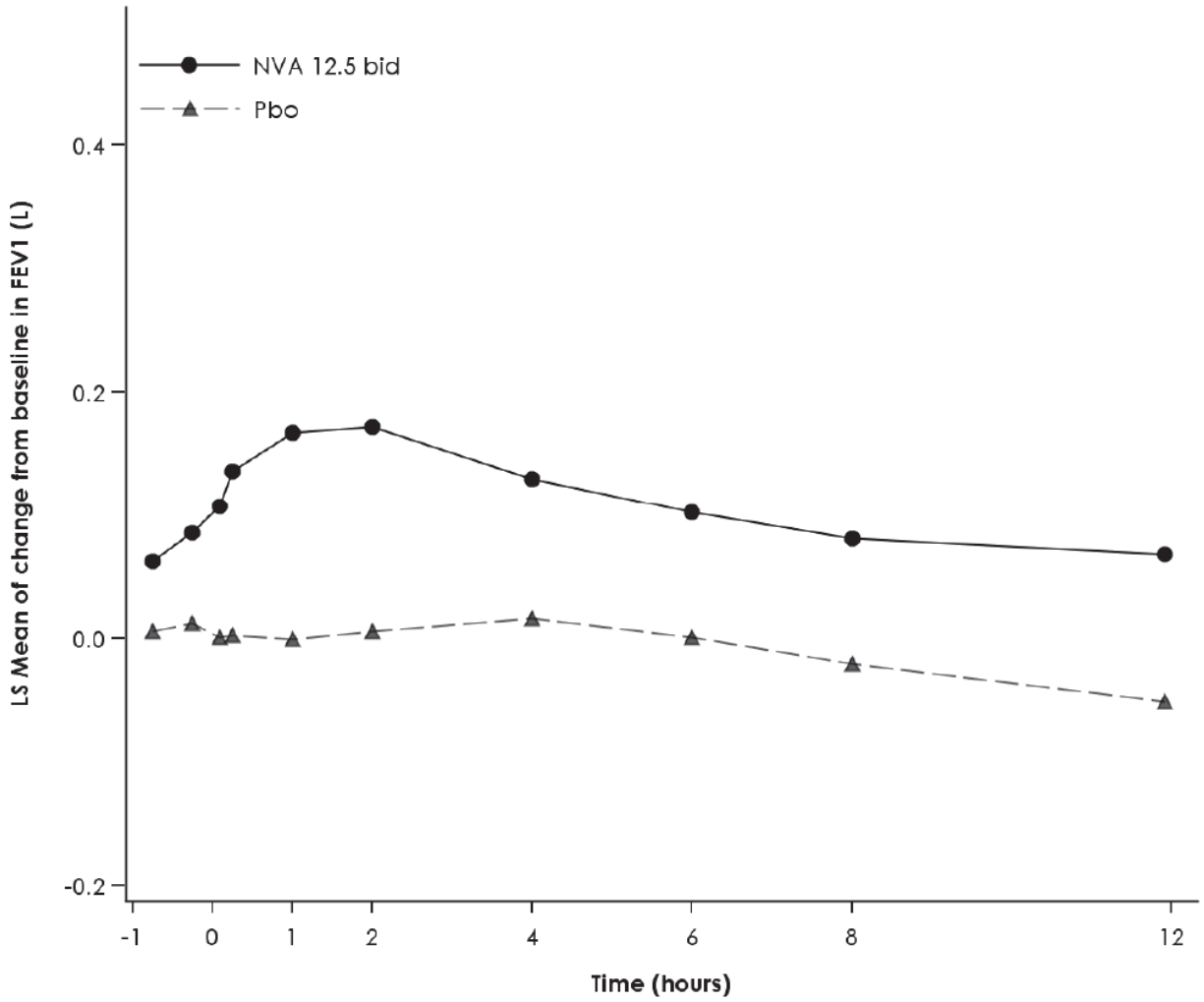


NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: Change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Separate MMRM were performed for each timepoint using visit as repeated variable.
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-3, Page 58

Figure 8. Change from baseline in FEV_1 (L) from -45 min to 11 h 55 min on Day 85 (FAS) – Study A2318



NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: Change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Separate MMRM were performed for each timepoint using visit as repeated variable.
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-4, Page 59

Sensitivity Analysis

For the phase 3 studies, the sponsor conducted multiple sensitivity analyses using patterns based on patient populations as outlined in Table 19.

Table 19. Primary Efficacy Endpoint Sensitivity Analysis Studies A2317 and A2318

	Study A2317	Study A2318
Population	**LS mean treatment differences**	
Per protocol set analysis	0.136 L	0.128 L
FAS analysis including data for patients who discontinued study treatment prematurely, but performed serial spirometry while not taking study drug	0.155 L	0.126 L
FAS analysis where a missing Week 12 value was imputed by carrying forward the Day 1 value	0.144 L	0.125 L
FAS analysis using a pattern mixture model for missing Week 12 data	0.139 L	0.122 L

FAS: full analysis set, an intent-to-treat [ITT] population
FAS analysis which included data for patients who discontinued study treatment prematurely but performed serial spirometry while not taking study drug.

Source: Module 2.7.3, Summary of Clinical Efficacy, page 55

The results of the sensitivity analyses based on the above populations were consistent with the primary efficacy analysis.

Studies A2336 and A2337

Studies A2336 and A2337 were conducted as part of the combination GP/Ind development program, and each included single-ingredient GP treatment arms as part of the typical factorial design. The single-ingredient GP and corresponding placebo arms from these trials provided supportive efficacy data.

Table 20. FEV_1 (L) AUC(0-12h) at Week 12 (FAS) – Study A2336 and Study A2337

				Treatment Difference		
Study Treatment	**Baseline FEV_1 Raw Mean**	**CFB FEV_1 AUC LS Mean (SE)**	**Comparison**	***LS Mean (SE)**	**(95% CI)**	**p-value**
Study A2336						
GPI 12.5/27.5 mcg BID N=258	1.263	0.211 (0.0140)	GPI-Ind	0.094 (0.0198)	(0.055, 0.133)	<.001
			GPI-GP	0.098 (0.0199)	(0.059, 0.137)	<.001
			GPI-Pbo	0.231 (0.0202)	(0.192, 0.271)	<.001
Ind 27.5 mcg BID N= 260	1.273	0.117 (0.0140)	Ind-Pbo	0.138 (0.0202)	(0.098, 0.177)	<.001
GP 12.5 mcg BID N=261	1.263	0.112 (0.0141)	GP-Pbo	0.133 (0.0202)	(0.093, 0.173)	<.001
Placebo N=260	1.260	-0.021 (0.0145)	-	-	-	-
Study A2337						
GPI 12.5/27.5 mcg BID N=249	1.247	0.234 (0.0134)	GPI-Ind	0.112 (0.0189)	(0.075, 0.149)	<.001
			GPI-GP	0.079 (0.0189)	(0.042, 0.116)	<.001
			GPI-Pbo	0.262 (0.0191)	(0.224, 0.300)	<.001
Ind 27.5 mcg BID N=251	1.235	0.122 (0.0134)	Ind-Pbo	0.150 (0.0192)	(0.112, 0.187)	<.001
GP 12.5 mcg BID N=250	1.260	0.155 (0.0134)	GP-Pbo	0.183 (0.0192)	(0.146, 0.221)	<0.001
Placebo N=246	1.231	-0.028 (0.0137)	-	-	-	-

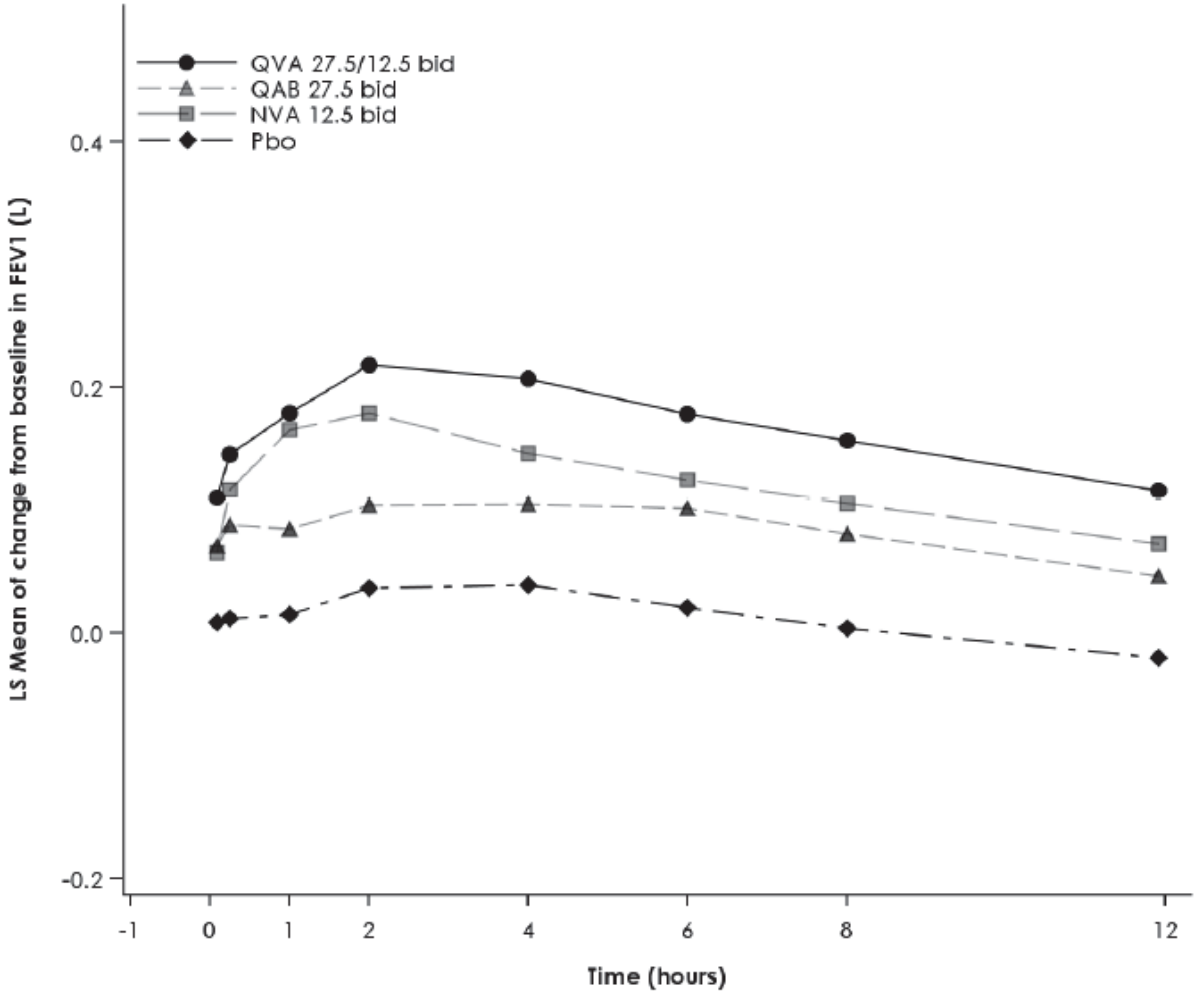
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from baseline, BL = baseline.
*All LS Means, SEs, CIs, and p-values are from a MMRM: change from baseline in FEV1 AUC = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Baseline raw means are not from the model.
Baseline FEV1 is defined as the average of the -45 min and -15 min FEV1 values taken on Day 1.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-20, page 55

As described in Table 20, the LS mean treatment difference for change from baseline in FEV_1 AUC(0-12h) was statistically significant for GP versus placebo at 12 weeks (0.13 L and 0.18 L, $p<0.001$, respectively) for both studies (A2336 and A2337).

Serial spirometric evaluations throughout the 12-hour dosing interval were performed in all subjects on Days 1 and 85 (Week 12), and are displayed in Figure 9 and Figure 10 for Study A2336 and in Figure 11 and Figure 12 for Study A2337, respectively. These FEV_1 profiles at the beginning and end of the treatment period provide support for the duration of treatment effect over the entire dosing interval.

Figure 9. Change from baseline in FEV_1 (L) from 5 min up to 11 h 55 min post-dose on Day 1 (FAS) – Study A2336

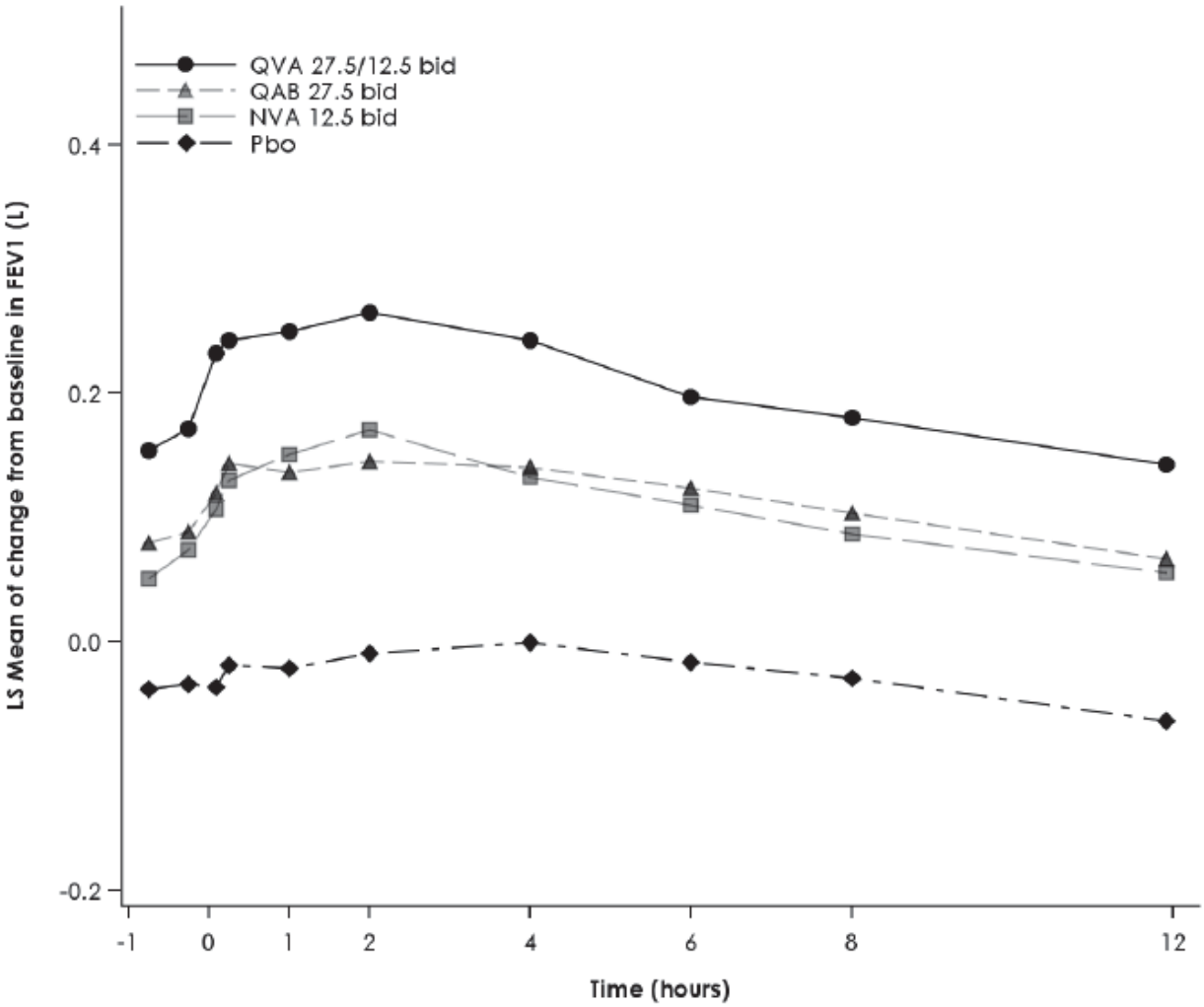


QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Separate MMRM were performed for each time point using visit as repeated variable.
Baseline is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1. Baseline values can be found in the source table.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-4, page 61

Figure 10. Change from baseline in FEV_1 (L) from -45 min to 11 h 55 min on Day 85 (FAS) – Study A2336

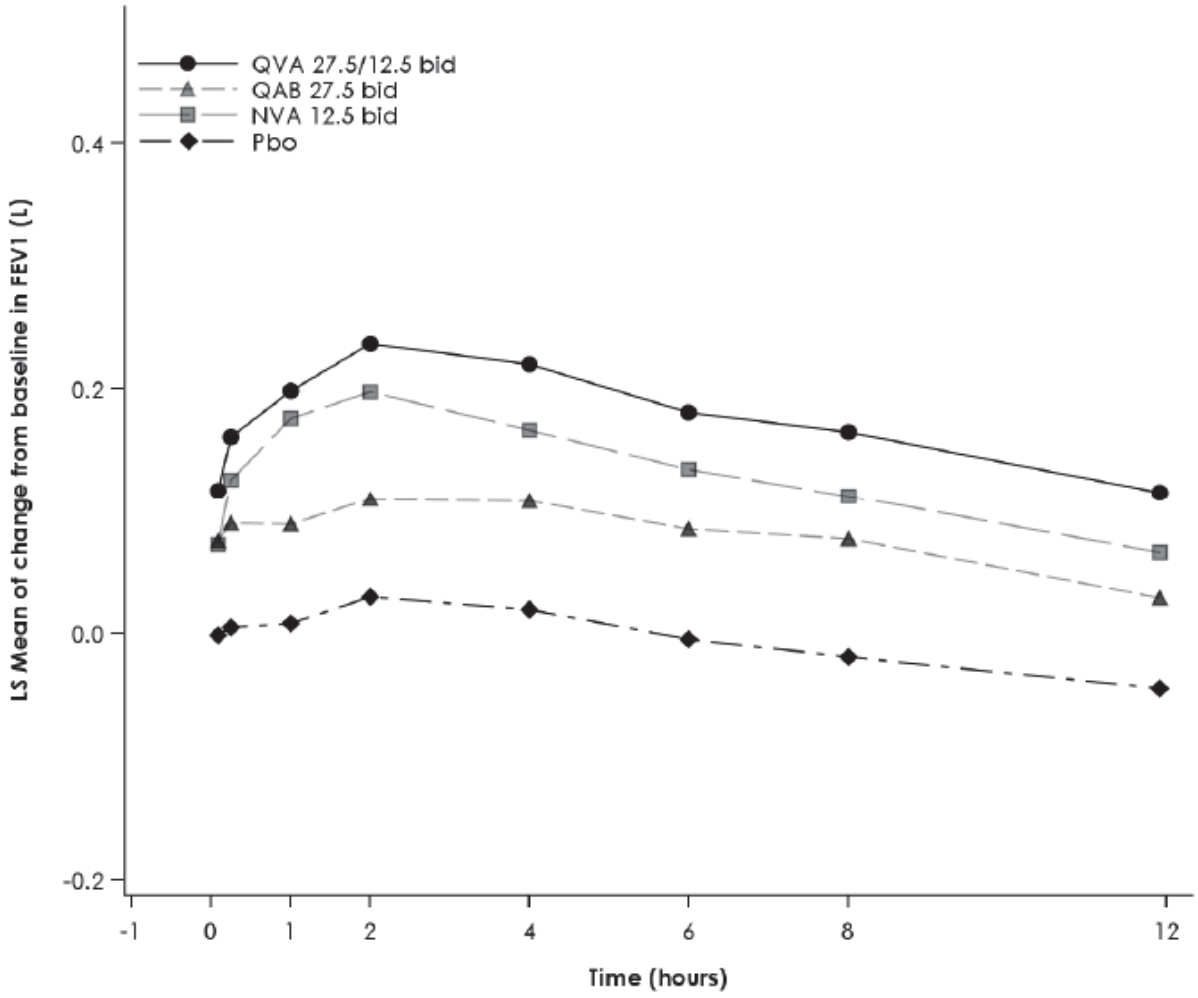


QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Separate MMRM were performed for each time point using visit as repeated variable.
Baseline is defined as the average of the pre-dose FEV1measured at -45 min and -15 min at Day 1.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-2, page 58

Figure 11. Change from baseline in FEV_1 (L) from 5 min up to 11 h 55 min post-dose on Day 1 (FAS) – Study A2337

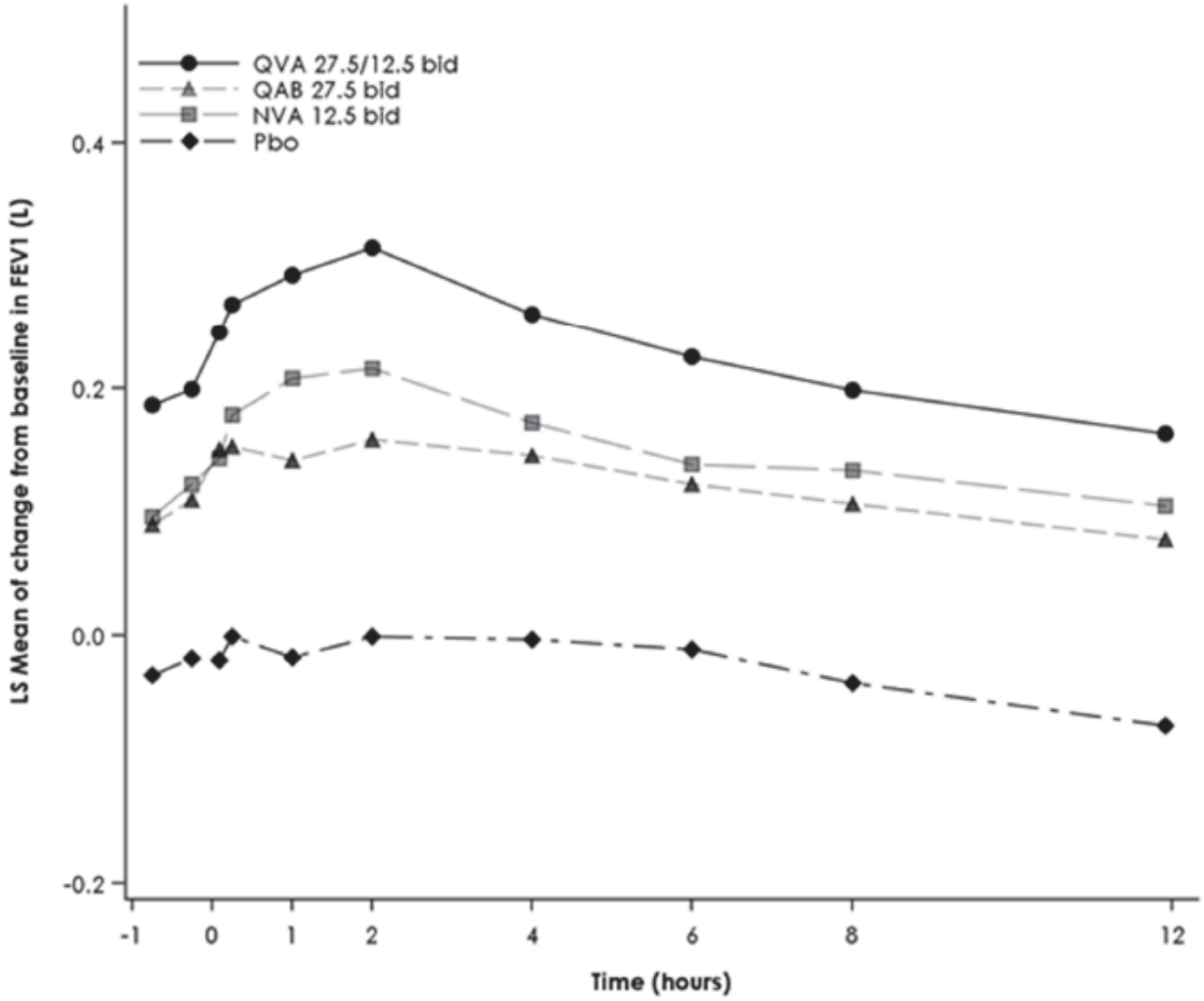


QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Separate MMRM were performed for each time point using visit as repeated variable.
Baseline is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1.
Baseline values can be found in the source table.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-3, page 60

Figure 12. Change from baseline in FEV_1 (L) from -45 min to 11 h 55 min on Day 85 (FAS) – Study A2337



QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: change from baseline in FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Separate MMRM were performed for each time point using visit as repeated variable.
Baseline is defined as the average of the pre-dose FEV1measured at -45 min and -15 min at Day 1.
Baseline values can be found in the source table.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-1, page 57

6.1.5 Analysis of Secondary Endpoints(s)

Studies A2317 and 2318

Trough FEV_1

Table 21. Trough FEV_1 (L) by visit (FAS) – A2317, A2318

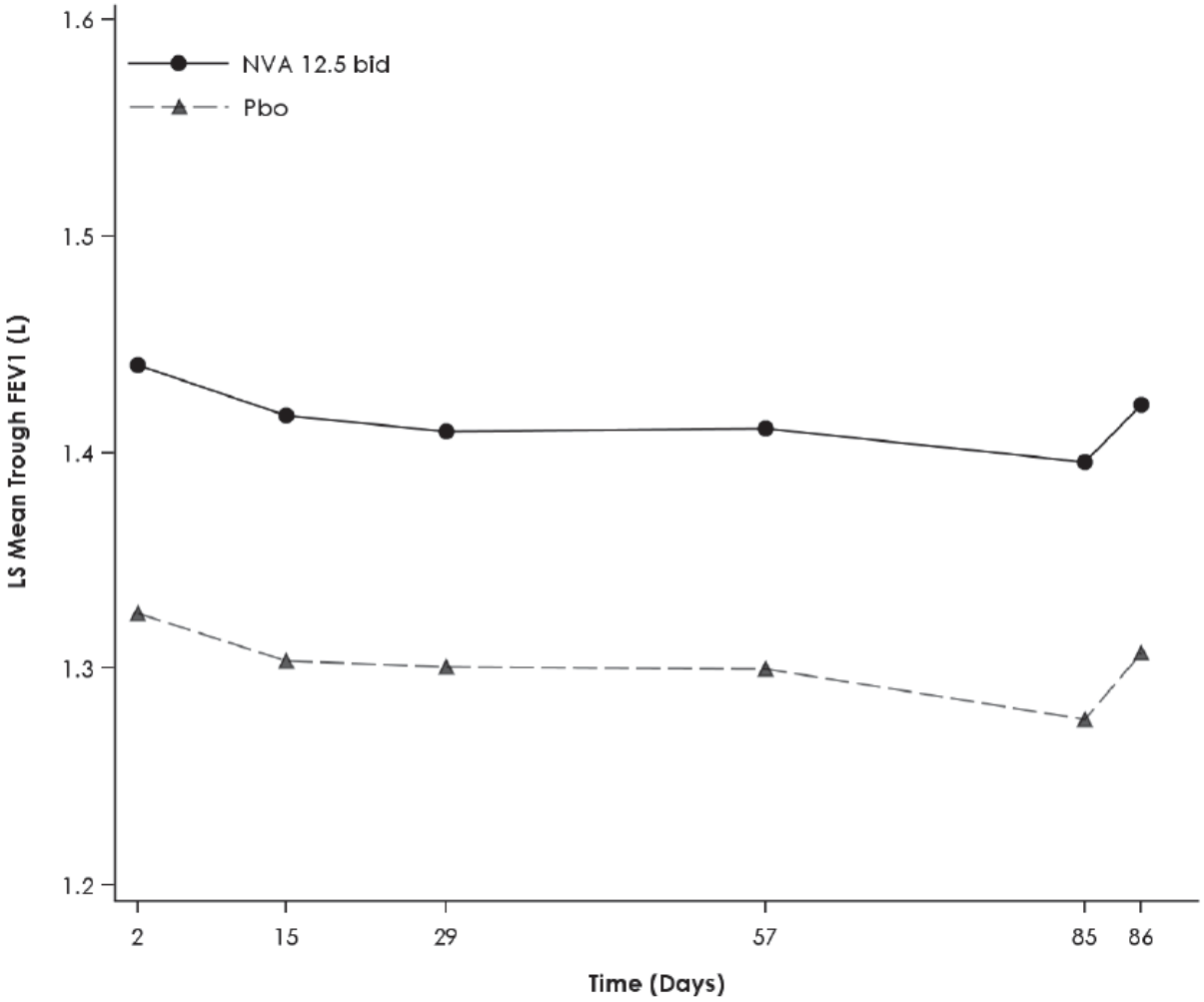
				Treatment Difference		
Day	**Treatment**	**CFB trough FEV_1 LS Mean (SE)**	**Comparison**	**LS Mean (SE)**	**(95% CI)**	**p-value**
Study A2317						
Trough FEV_1						
Day 2	GP 12.5 mcg BID N=218	0.141 (0.0124)	GP– Placebo	0.115 (0.0162)	(0.083, 0.147)	<0.001
	Placebo N=214	0.025 (0.0122)				
Day 86	GP 12.5 mcg BID N=218	0.123 (0.0171)	GP– Placebo	0.115 (0.0235)	(0.069, 0.162)	<0.001
	Placebo N=214	0.007 (0.0173)				
Study A2318						
Trough FEV_1						
Day 2	GP 12.5 mcg BID N=213	0.128 (0.0129)	GP– Placebo	0.107 (0.0177)	(0.072, 0.142)	<0.001
	Placebo N=208	0.021 (0.0130)				
Day 86	GP 12.5 mcg BID N=213	0.123 (0.0166)	GP– Placebo	0.086 (0.0230)	(0.041, 0.131)	<0.001
	Placebo N=208	0.038 (0.0166)				

CFB: change from baseline
MMRM: change from baseline in (pre-dose) trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment * visit interaction + baseline FEV1 * visit interaction.
MMRM performed for trough FEV1
Baseline FEV1 was defined as the average of the -45 min and -15 min FEV1 values taken on Day 1.
Trough FEV1 was defined as the mean of FEV1 at 23 h 15 min and 23 h 45 min after the morning dose of the previous day.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-21, page 60, Table 3-22, page 61

As shown in Table 21, in both studies A2317 and A2318, the mean treatment differences for trough FEV_1 (change from baseline) were statistically significant at all times, demonstrating efficacy beginning with the first dose which was maintained at 12 weeks.

Figure 13. Trough and pre-dose trough FEV_1 (L) over visits (FAS) – Study A2317



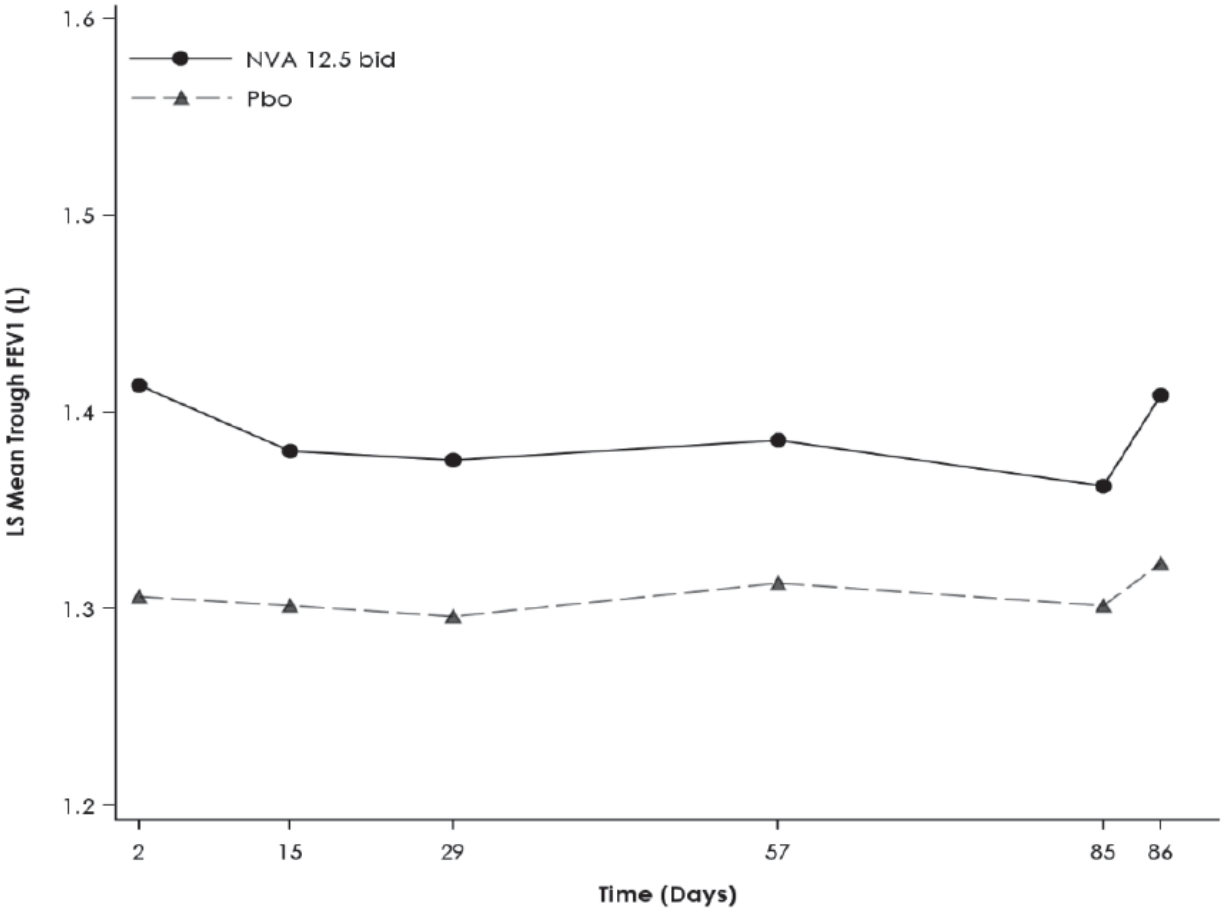
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: (Pre-dose) trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Two separate MMRM were performed for trough FEV1 and pre-dose trough FEV1.
Trough FEV1 (Days 2 and 86) is defined as the mean of FEV1 at 23 h 15 min and 23 h 45 min.
Pre-dose trough FEV1 (Days 15, 29, 57, 85) is defined as the mean of FEV1 at -45min and -15 min.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-5, Page 62

The results are displayed graphically in Figure 13 for study A2317 and in Figure 14 for study A2318, respectively. These graphs demonstrate clear separation between the curves for trough FEV1 between GP and placebo throughout the entire treatment period.

Figure 14. Trough FEV_1 and pre-dose trough (L) over visits (FAS) – Study A2318



NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: (Pre-dose) trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction.
Two separate MMRM were performed for trough FEV1 and pre-dose trough FEV1.
Trough FEV1 (Days 2 and 86) is defined as the mean of FEV1 at 23 h 15 min and 23 h 45 min.
Pre-dose trough FEV1 (Days 15, 29, 57, 85) is defined as the mean of FEV1 at -45min and -15 min.

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-6, Page 63

Studies A3336 and A2337

Trough FEV1

Table 22. Trough FEV_1 (L) at Day 86 – Study A2336, A2337

				Treatment Difference		
Day	**Treatment**	**CFB trough FEV_1 LS Mean (SE)**	**Comparison**	**LS Mean (SE)**	**(95% CI)**	**p-value**
Study A2336						
Trough FEV_1						
Day 86	GPI 12.5/27.5 mcg BID N=256	0.201 (0.0144	GPI-Ind	0.081 (0.0202)	(0.041, 0.121)	<0.001
			GPI-GP	0.110 (0.0202)	(0.070, 0.149)	<0.001
			GPI-Pbo	0.213 (0.0208)	(0.173, 0.254)	<0.001
	Ind 27.5 mcg BID N=257	0.120 (0.0142)	Ind-Pbo	0.133 (0.0207)	(0.092, 0.173)	<0.001
	GP 12.5 mcg BID N=260	0.092 (0.0142)	GP-Pbo	0.104 (0.0206)	(0.063, 0.144)	<0.001
	Placebo N=252	-0.012 (0.0150)	-	-	-	-
Study A2337						
Trough FEV_1						
Day 86	GPI 12.5/27.5 mcg BID N=246	0.216 (0.0142)	GPI-Ind	0.078 (0.0199)	(0.039, 0.117)	<0.001
			GPI-GP	0.087 (0.0200)	(0.048, 0.127)	<0.001
			GPI-Pbo	0.233 (0.0202)	(0.193, 0.273)	<0.001
	Ind 27.5 mcg BID N=251	0.138 (0.0141)	Ind-Pbo	0.155 (0.0202)	(0.116, 0.195)	<0.001
	GP 12.5 mcg BID N=249	0.128 (0.0142)	GP-Pbo	0.146 (0.0203)	(0.106, 0.185)	<0.001
	Placebo N=245	-0.017 (0.0145)	-	-	-	-

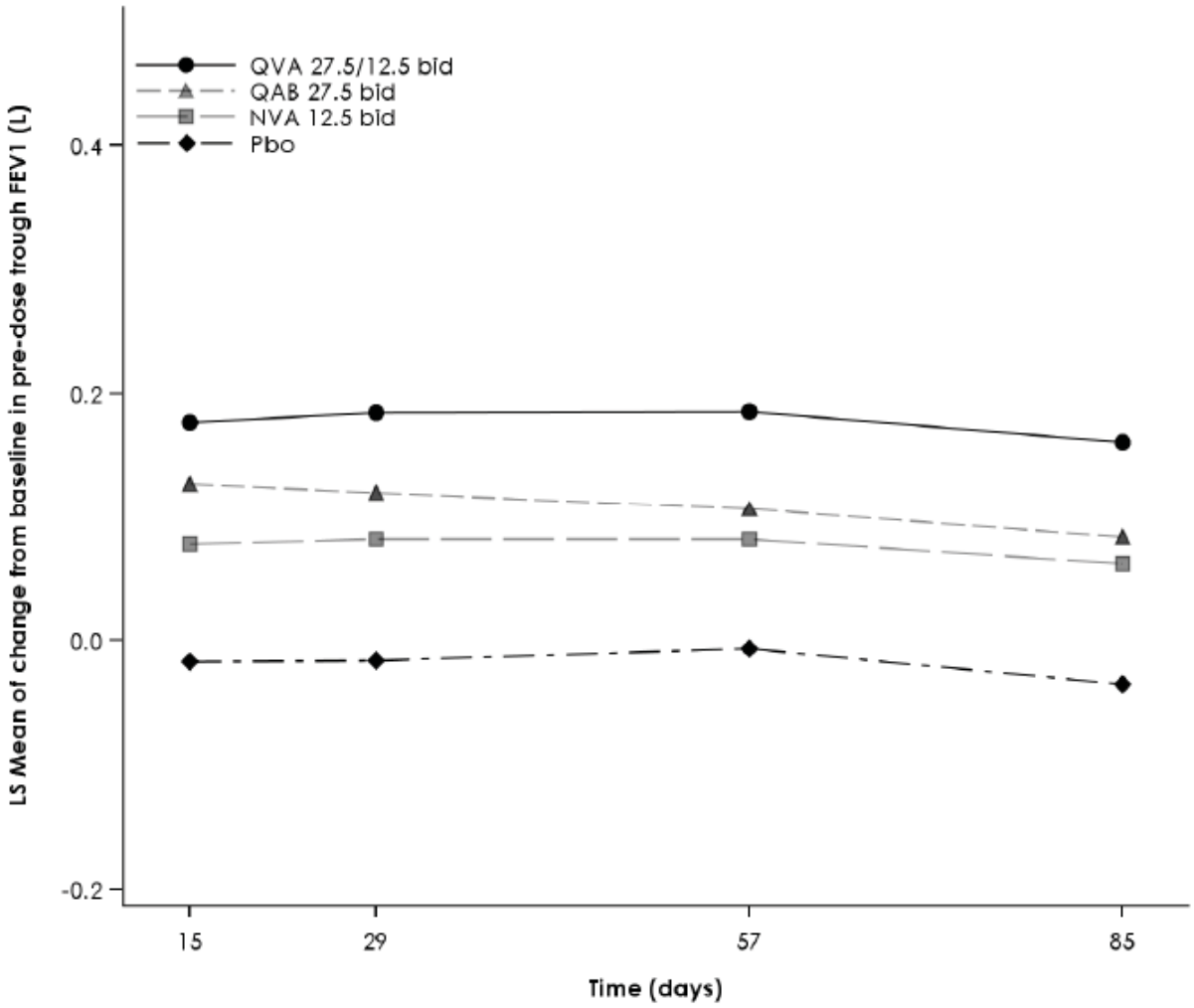
LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval, CFB = change from baseline, Pbo= placebo.
All LS Means, SEs, CIs, and p-values are from a MMRM: change from baseline in trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region. Baseline raw means are not from the model.
Baseline FEV1 is defined as the average of the -45 min and -15 min FEV1 values taken on Day 1.
Trough FEV1 is defined as the mean of FEV1 at 23 h 15 min and 23 h 45 min after the morning dose of the previous day.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-23, page 65

As shown in Table 22, in both studies A2336 and A2337, the mean treatment differences for trough FEV_1 (change from baseline) were statistically significant on day 86 demonstrating efficacy was maintained at 12 weeks.

The results are displayed graphically in Figure 15 for study A2336 and in Figure 16 for study A2337, respectively. These graphs demonstrate clear separation between the curves for trough FEV_1 between GPI, Ind, GP and placebo throughout the entire treatment period.

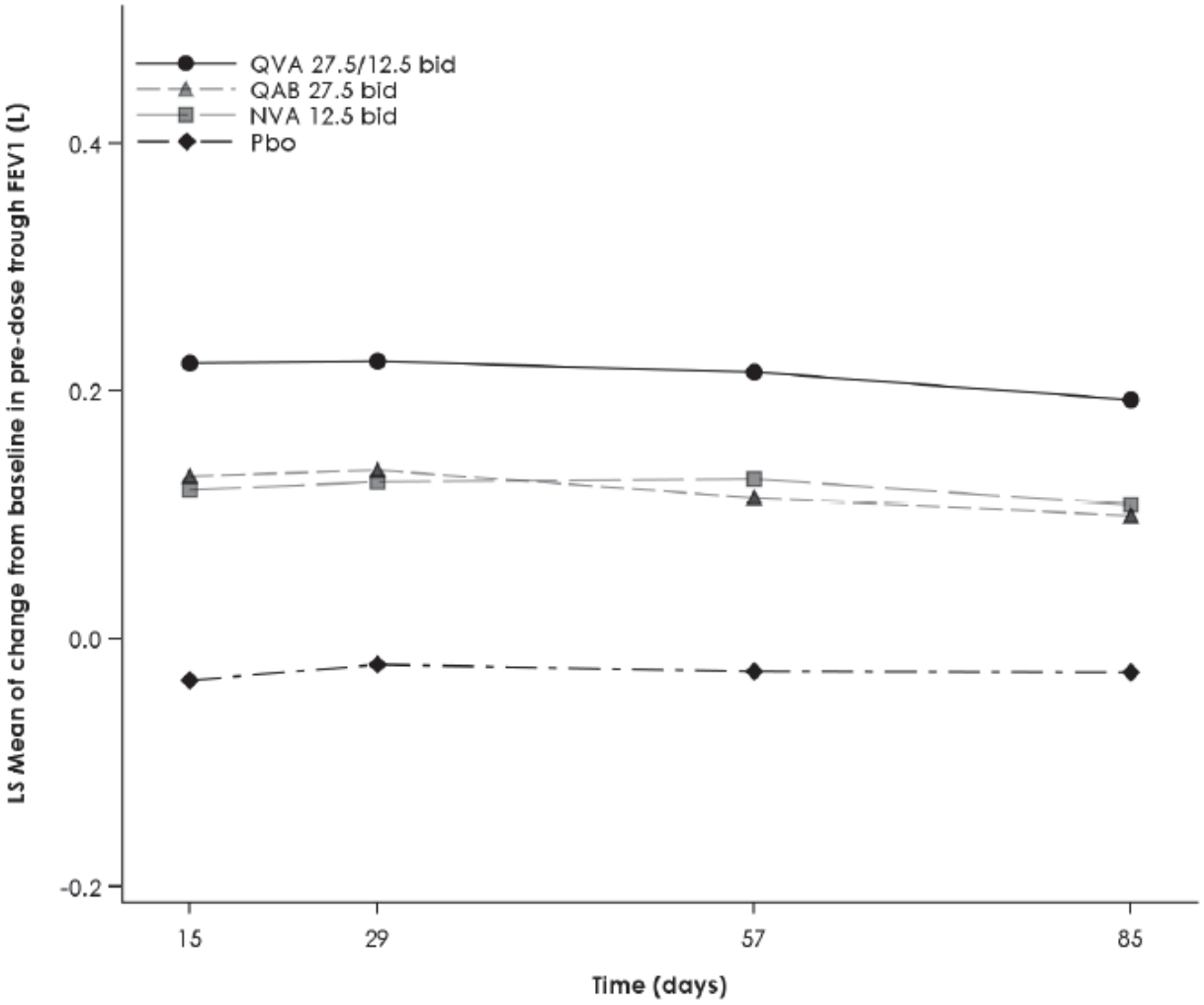
Figure 15. Pre-dose trough FEV1 (L) change from baseline over visits (FAS) – Study A2336



QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo
Estimates obtained from MMRM: change from baseline in pre-dose trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Baseline is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1

Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-6, page 64

Figure 16. Pre-dose trough FEV1 (L) change from baseline over visits – Study A2337



QVA 27.5/12.5 BID= GPI 12.5/27.5 mcg BID
QAB 27.5 BID= Ind 27.5 mcg BID
NVA 12.5 BID= GP 12.5 mcg BID
Pbo= placebo

Estimates obtained from MMRM: change from baseline in pre-dose trough FEV1 = treatment + baseline FEV1 + smoking status at baseline + baseline ICS use + visit + treatment*visit interaction + baseline FEV1*visit interaction + region.
Baseline is defined as the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1.
Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 3-5, page 63

Multiple other secondary efficacy endpoints were analyzed. The other secondary endpoints for the phase 3 studies are grouped under the following categories: further analyses on lung function, patients reported outcomes (PRO) and onset of action. Secondary endpoints will be presented in this section under their respective categories.

Lung Function

FEV_1 AUC

The change from baseline in FEV_1 AUC 0-4h, AUC 4-8h, AUC 8-12h, AUC 0-12h at Day 1 and Week 12 (Day 85) were measured in both studies. GP demonstrated statistically significant improvements versus placebo at each time point ($p<0.001$) in both studies.

Trough FVC

In Study A2317, the LS mean treatment differences for change from baseline in trough FVC was 0.163 L on Day 2 and 0.140 L at Week 12 (Day 86), ($p<0.001$). Statistically significant changes from baseline favoring GP in pre-dose trough FVC were observed at all time points during the study (LS mean treatment differences: Day 15: 0.173 L, Day 29: 0.152 L, Day 57: 0.172 L, Day 85: 0.193 L [$p<0.001$]).

In Study A2318, the LS mean treatment differences for change from baseline in trough FVC was 0.171 L on Day 2 and 0.130 L at Week 12 (Day 86), ($p<0.001$). Statistically significant changes from baseline favoring GP in pre-dose trough FVC were observed at all time points during the study (LS mean treatment differences: Day 15: 0.124 L, Day 29: 0.145 L, Day 57: 0.137 L, Day 85: 0.118 L [$p<0.001$]).

PRO

SGRQ

Table 23. SGRQ total and component scores (change from baseline) at Week 12 (FAS) – Study A2317, A2318

Treatment		CFB in SGRQ score LS Mean (SE)	Comparison	Treatment Difference LS Mean (SE)	(95% CI)	p-value
Study A2317						
Total Score	GP 12.5 mcg BID N=210	-4.4 (0.96)	GP– Placebo	-2.8 (1.14)	(-5.0, -0.5)	0.016
	Placebo N=192	-1.7 (0.96)				
Symptoms Component Score	GP 12.5 mcg BID N=210	-8.0 (1.43)	GP– Placebo	-3.8 (1.66)	(-7.0, -0.5)	0.025
	Placebo N=193	-4.3 (1.43)				
Activity Component Score	GP 12.5 mcg BID N=210	-3.7 (1.13)	GP– Placebo	-4.2 (1.36)	(-6.9, -1.5)	0.002
	Placebo N=193	0.5 (1.13)				
Impacts Component Score	GP 12.5 mcg BID N=210	-3.8 (1.04)	GP– Placebo	-2.0 (1.31)	(-4.6, 0.6)	0.128
	Placebo N=192	-1.8 (1.04)				
Study A2318						
Total Score	GP 12.5 mcg BID N=193	-6.4 (1.08)	GP– Placebo	-5.2 (1.28)	(-7.7, -2.7)	<0.001
	Placebo N=194	-1.2 (1.06)				
Symptoms Component Score	GP 12.5 mcg BID N=194	-9.6 (1.37)	GP– Placebo	-5.2 (1.62)	(-8.4, -2.0)	0.002
	Placebo N=195	-4.4 (1.34)				
Activity Component Score	GP 12.5 mcg BID N=195	-4.0 (1.19)	GP– Placebo	-3.8 (1.45)	(-6.7, -1.0)	0.009
	Placebo N=195	-0.1 (1.17)				
Impacts Component Score	GP 12.5 mcg BID N=194	-6.5 (1.23)	GP– Placebo	-5.7 (1.52)	(-8.7, -2.7)	<0.001
	Placebo N=194	-0.8 (1.20)				

CFB: Change from baseline
LMM: (linear mixed model) change from baseline in SGRQ score= treatment + baseline SGRQ score + smoking status at baseline + baseline ICS use + random center effect.
Missing Week 12 data were imputed with last observation carried forward (LOCF) but only if measured at Day >=29 (LOCF data may come from unscheduled or premature discontinuation visits).
Source: Module 2.7.3, Summary of Clinical Efficacy, Table 3-26, page 67, Table 3-27, page 68

In both pivotal phase 3 studies (A2317 and A2318) at week 12, the difference in SGRQ total score was statistically better in the GP treatment arms as compared with placebo (-2.8, 95% CI [-5, -0.5] and -5.2, 95%CI [-7.7, -2.7], respectively). In both studies, the GP treatment arm achieved a change from baseline in the SGRQ total score that exceeded the MCID of -4 units (-4.4 and -6.4, respectively).

Figure 17. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ total score at week 12- Study A2317

	NVA 237 12.5 b.i.d N=222		Placebo N=216
n/M (%)	103/210 (49)		78/192 (41)
Odds Ratio		1.43	
95% CI		0.95, 2.15	
p-value		0.083	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number CNVA237A2317 Table 11-11, page 107

Original figure generated by Kiya Hamilton, PhD, statistical reviewer.

As can be seen in the table above, when analyzed via a responder analysis, where a response was defined as those patients who achieved and MCID of -4, GP did not demonstrate a statistically significant effect vs. placebo (OR: 1.43, 95% CI [0.95, 2.15]).

Figure 18. Proportion of patients with a clinically important improvement of at least 4 units in the SGRQ total score at week 12- Study A2318

	NVA 237 12.5 b.i.d N=215		Placebo N=214
n/M (%)	106/193 (55)		82/194 (42)
Odds Ratio		1.78	
95% CI		1.17, 2.71	
p-value		0.008	

N: Number of observations used in the analysis
Source: Clinical Trial Report-Protocol Number CNVA237A2318 Table 11-11, page 108
Original figure generated by Kiya Hamilton, PhD, statistical reviewer.

As can be seen in the table above, when analyzed via a responder analysis, where a response was defined as those patients who achieved and MCID of -4, GP demonstrated a statistically significant effect vs. placebo (OR: 1.78, 95% CI [1.17, 2.71]).

Rescue Medication

In both studies A2317 and A2318, statistically significant reductions in the mean daily number of puffs, mean daytime number of puffs, and mean nighttime number of puffs of rescue medication were shown with GP compared with placebo. Study A2317 also demonstrated statistically significant increases in the percentage of days with no rescue medication use for GP.

Onset of Action

Time to onset of action was defined as the duration (in minutes) from inhalation of study drug to a ≥ 0.100 L increase in FEV_1 from baseline on Day 1. The median time to onset of action was 18.8 minutes and 20.5 minutes for patients taking GP in studies A2317 and A2318, respectively. The time to onset of action was statistically significantly shorter ($p<0.001$) when GP was compared to placebo in both studies.

Reviewer's Comment: Note that time to onset was defined by the sponsor and is of uncertain clinical significance, particularly in this chronically administered drug.

6 Other Endpoints

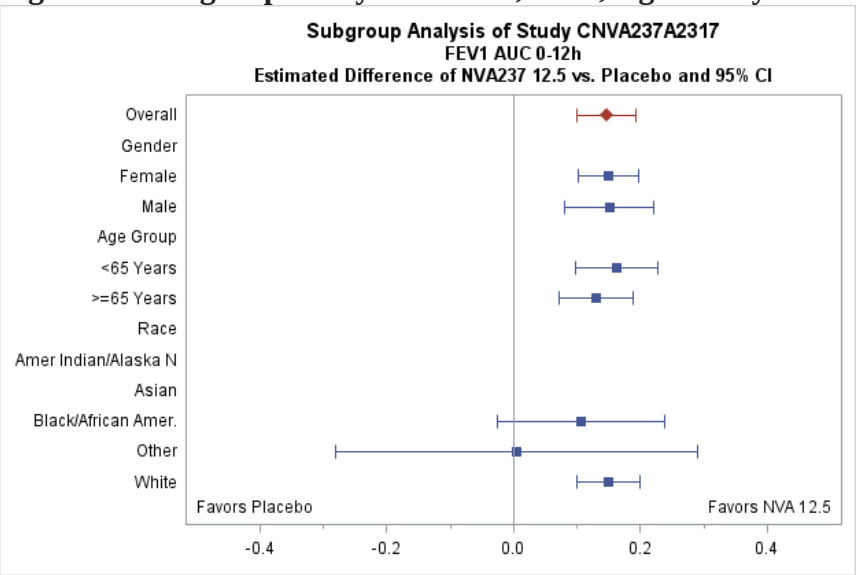
6.1.7 Subpopulations

Subgroup analysis on the primary and key secondary efficacy endpoints are shown by gender, age, race (Black or African American, American Indian or Alaskan Native, Asian, White, and Other), airflow limitation, smoking status, and ICS use in studies 2317 and 2318 only. The subgroup analyses were performed using the FAS population.

Gender, Race, and Age

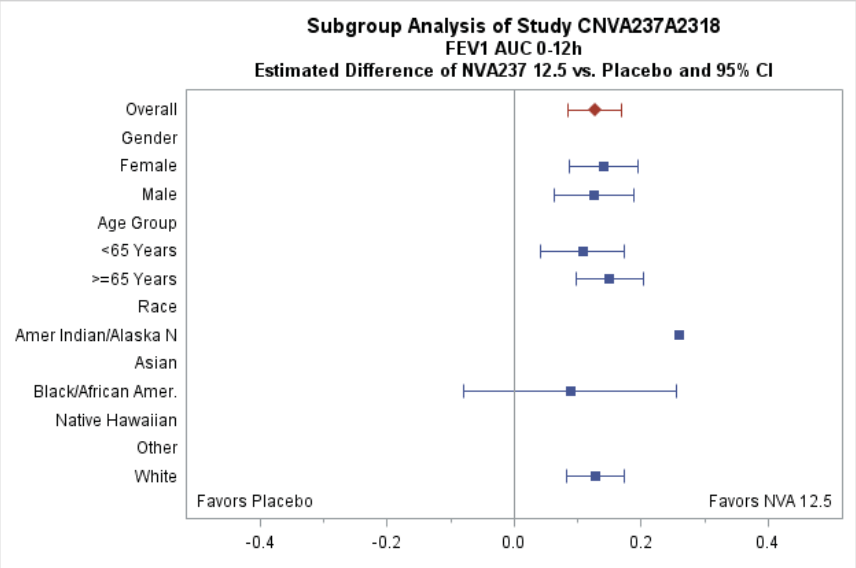
Figures 19 and 20 below summarize the efficacy results by subgroups for studies 2317 and 2318 for gender, race, and age. In general, the subgroup analyses were consistent with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 19. Subgroup Analysis Gender, Race, Age- Study A2317



NVA237= GP 12.5 mcg BID
Source: Statistical Review, Dr. Kiya Hamilton

Figure 20. Subgroup Analysis Gender, Race, Age- Study A2318

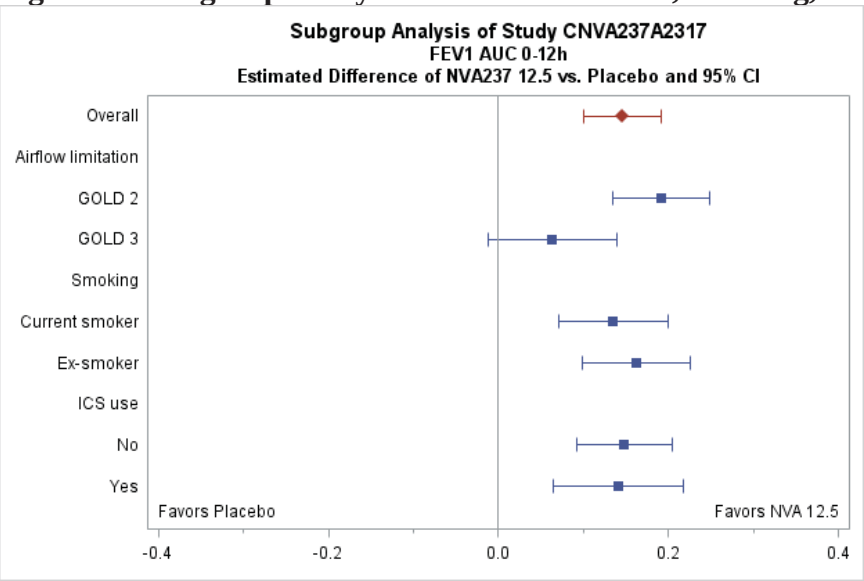


NVA237= GP 12.5 mcg BID
Source: Statistical Review, Dr. Kiya Hamilton

Figures 21 and 22 below summarize the efficacy results by subgroups for studies 2317 and 2318 for airflow limitation, smoking, and ICS use. In general, the subgroup analyses were consistent

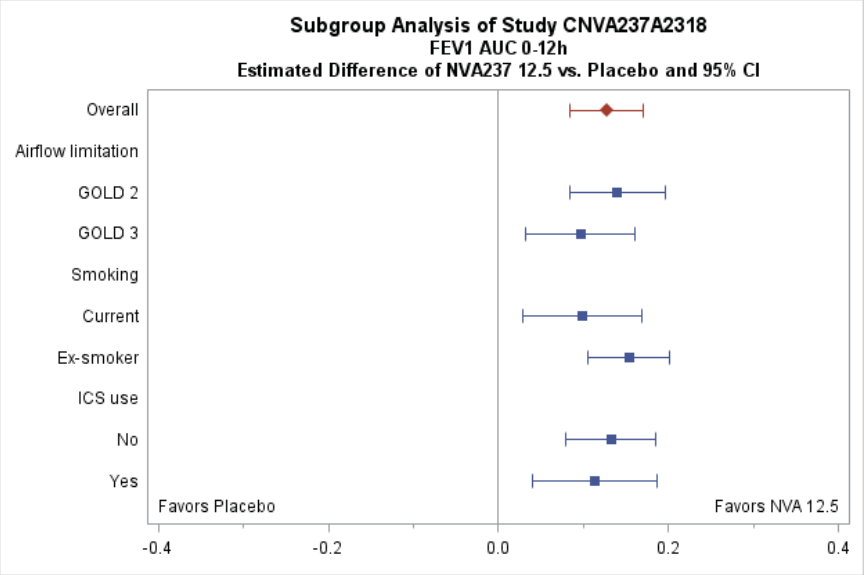
with the primary and key secondary results from the overall population. However, these studies were not designed or powered to detect differences in these specific groups.

Figure 21. Subgroup Analysis Airflow Limitation, Smoking, and ICS use- Study 2317



NVA237= GP 12.5 mcg BID
Source: Statistical Review, Dr. Kiya Hamilton

Figure 22. Subgroup Analysis Airflow Limitation, Smoking, and ICS use- Study 2318



NVA237= GP 12.5 mcg BID
Source: Statistical Review, Dr. Kiya Hamilton

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study A2208

A2208 was a multicenter, 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 GP treatments studied were QD (12.5 mcg QD, 25 mcg QD, 50 mcg QD and 100 mcg QD), and BID (12.5 mcg BID, 25 mcg BID, and 50 mcg BID), and placebo administered over 28 days each.

The study population consisted of 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 FEV1 ≥30% and < 80% of the predicted normal, and post-bronchodilator FEV1/FVC < 0.7 at Visit 2 (Post refers to 45 mins after inhalation of 84 µg ipratropium bromide). Symptomatic patients, according to daily electronic diary data between Visit 2 and Visit 3, with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3.

The primary analysis variable was trough FEV1 (calculated as the average of the 23h 15min and 23h 45min measurements).

Baseline demographics were comparable between treatment groups. In total, the mean age of the patients was 61.2 years, with approximately two-thirds of patients being <65 years of age. Approximately two-thirds of patients were male and 85.0% were Caucasian. The majority of patients (74.4%) had a BMI ≤30 kg/m2. The mean duration of COPD was 7.7 years, and the majority of patients had disease duration of 1 to 5 years (32.9% of patients) or >5 to 10 years (30.3% of patients). Patients either had moderate COPD (58.0% of patients) or severe COPD (42.0%) according to GOLD 2008. Most patients (78.5%) did not have a COPD exacerbation history at baseline. Approximately 62% of patients used ICS. Just over half of patients were ex-smokers. The mean estimated number of pack years was 41.0. There were no meaningful differences between treatment groups for spirometry measurements at screening. Baseline vital signs and ECGs were comparable across treatment groups. The overall population was similar to the phase 3 trials.

Table 24. Subject Disposition A2208

Disposition Reason	GP 12.5 mcg QD n (%)	GP 25 mcg QD n (%)	GP 12.5 mcg BID n (%)	GP 50 mcg QD n (%)	GP 25 mcg BID n (%)	GP 100 mcg QD n (%)	GP 50 mcg BID n (%)	Placebo n (%)	Total
Screened									542
Randomized	96	99	99	96	100	98	94	94	388
Exposed	89 (92.7)	96 (97.0)	95 (96.0)	92 (95.8)	96 (96.0)	96 (98.0)	87 (92.6)	91 (96.8)	386 (99.5)
Completed	80 (83.3)	91 (91.9)	93 (93.9)	89 (92.7)	89 (89.0)	92 (93.9)	82 (87.2)	82 (87.2)	341 (87.9)
Discontinued	11 (11.5)	5 (5.1)	2 (2.0)	3 (3.1)	7 (7.0)	4 (4.1)	6 (6.4)	9 (9.6)	48 (12.4)
Primary reason for discontinuation									
Adverse event	6 (54.5)	3 (60.0)	1 (50.0)	0	6 (85.7)	3 (75.0)	2 (33.3)	4 (44.4)	25 (52.1)
Withdrew consent	1 (9.1)	1 (20.0)	0	2 (66.7)	0	0	1 (16.7)	4 (44.4)	9 (18.8)
Protocol deviation	2 (18.2)	0	0	0	0	0	2 (33.3)	1 (11.1)	5 (10.4)
Lost to follow up	2 (18.2)	0	0	0	0	1 (25.0)	1 (16.7)	0	4 (8.3)
Administrative problems	0	1 (20.0)	1 (50.0)	0	0	0	0	0	3 (6.3)
Abnormal laboratory value(s)	0	0	0	0	1 (14.3)	0	0	0	1 (2.1)
Death	0	0	0	1 (33.3)	0	0	0	0	1 (2.1)

Note: 3 patients were randomized in error and discontinued within the screening period.
For completed row: only patients who completed both periods were counted in the Total column.
There was 1 non-randomized patient who was given study medication in error on Visit 3/4 and was discontinued. This patient is represented in the exposure total column and is not represented in a treatment groups column as these comprise the randomized set.
Since this was a crossover study, a patient could be counted in more than one of the treatment groups and the sum of the treatment groups is not equal to the number of patients in the Total column.
Percentages of patients completed and discontinued are calculated using the number of randomized patients as the denominator.
All other percentages in this table are based on the number of discontinued patients as the denominator.

Source: Module 5.3.5 Study A2208 CSR, Table 10-1, p 107

Table 25. Analysis of covariance of trough FEV1 (L) at Day 28 (FAS) – Study A2208

			Treatment Difference		
Treatment	**n**	**LS Mean (SE)**	**LS Mean (SE)**	**(95% CI)**	**p-value**
GP 12.5 mcg QD N=89	81	1.33 (0.02)	0.08 (0.03)	(0.030, 0.136)	0.002
GP 25 mcg QD N=96	88	1.34 (0.02)	0.09 (0.03)	(0.048, 0.148)	<0.001
GP 12.5 mcg BID N=95	90	1.39 (0.02)	0.14 (0.03)	(0.089, 0.189)	<0.001
GP 50 mcg QD N=92	88	1.34 (0.02)	0.09 (0.03)	(0.038, 0.142)	<0.001
GP 25 mcg BID N=96	87	1.41 (0.02)	0.17 (0.03)	(0.115, 0.219)	<0.001
GP 100 mcg QD N=96	90	1.42 (0.02)	0.18 (0.02)	(0.132, 0.220)	<0.001
GP 50 mcg BID N=87	81	1.42 (0.02)	0.18 (0.02)	(0.132, 0.222)	<0.001
Placebo N=91	82	1.25 (0.02)	-	-	-

The model has been adjusted for the following covariates: period baseline FEV1 measurement, FEV1 prior to inhalation and FEV1 45 min post-inhalation of ipratropium bromide, smoking status, baseline ICS use, and period. Patient is included as a random effect.
The analysis excluded values taken within 6 hours of rescue medication or 7 days of systemic corticosteroid use.
The period baseline FEV1 is the mean of the 45 and 15 minutes pre-dose FEV1 values at each period. Trough FEV1 is defined as the mean of the FEV1 values measured at 23 hours 15 min and 23 hours 45 min post-dose.

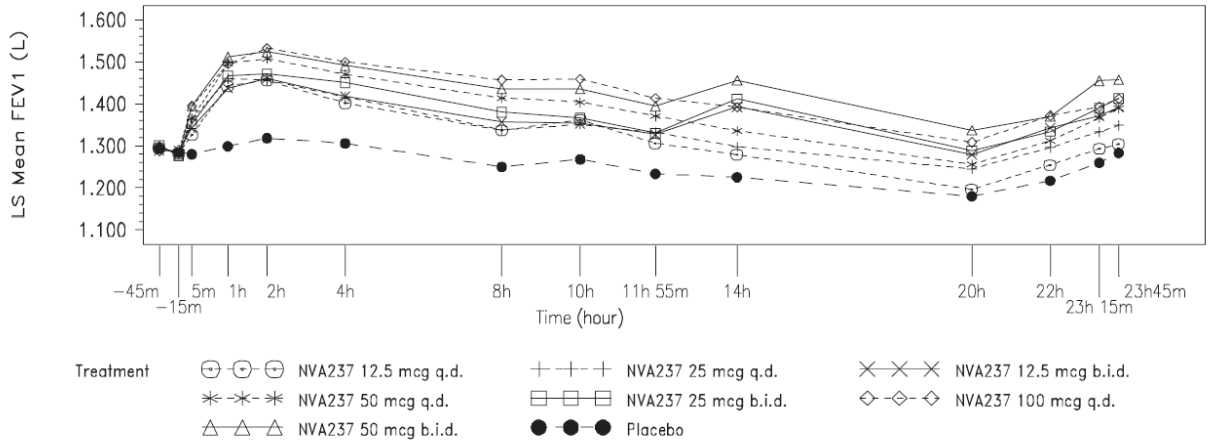
Source: Module 2.7.3, Summary of Clinical Efficacy, Table 4-1, page 104

Efficacy

Based on an ANCOVA analysis, at Day 28, all GP doses had a statistically significantly higher mean trough FEV_1 when compared to placebo (all p<0.001, with the exception of the comparison of GP 12.5 mcg QD vs placebo at Day 28; p=0.002). Treatment differences in trough FEV_1 after 28 days of dosing for all GP doses compared to placebo ranged from 0.083 L for the 12.5 mcg QD treatment regimen to 0.177 L for 50 mcg BID. The difference versus placebo for the 12.5 mcg BID treatment regimen, was 0.139 L.

The ANCOVA analyses demonstrated that the GP 12.5 mcg BID dose was an effective and clinically relevant dose and that it was safe and well tolerated. Based on the outcome of studies A2208 and A2205 and discussions with the Agency regarding the observed safety signal of atrial fibrillation and flutter, the GP 12.5 mcg BID dosing regimen was selected for further evaluation for the US pivotal Phase 3 studies.

Figure 23. 24-hour profile of least squares means of FEV1 (L) at Days 1/2, Days 7/8, Days 14/15 and Days 28/29, by treatment regimen (FAS)



The model has been adjusted for the following covariates: period baseline FEV1 measurement, FEV1 prior to inhalation and FEV1, 45 min post inhalation of ipratropium bromide, smoking status, baseline ICS use, and period. Patient is included as a random effect.
Note: analysis excluded values taken within 6 hours of rescue medication or 7 days of systemic corticosteroid use.

Source: CSR A2208, Page 818 Figure 14.2-12.1.1

The 24 hour profile of least square means of FEV1 for all studied doses is displayed in Figure 23. The 12.5 mcg BID dose shows clear separation form placebo and performed similarly to the 50 mcg QD and 25 mcg BID doses.

Based upon the efficacy findings and the safety signal identified for GP doses greater than 25 mcg QD (discussed in 7.2.2 Explorations for Dose Response), we agree with the dose selection of GP 12.5 mcg BID. (b) (4) .

For additional information, refer to Section 7.2.2 Explorations for Dose Response.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The two replicate phase 3 trials (A2317 and A2318) demonstrated persistence of response to GP over a 12 week treatment period. The spirometry endpoints in each controlled efficacy trial showed that GP 12.5 mcg BID produced statistically significant bronchodilation compared with placebo at the majority of the measured time-points post-dose over 24 hours. Figure 13 and Figure 14 (discussed in Section 6.1.4 Analysis of Primary Endpoint(s) shows the trough

FEV_1 through day 86 and demonstrates separation of the GP and placebo curves throughout the entire treatment period.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety evaluation of GP relies on 3-month data from 4 studies; A2317, A2318, A2336, and A2337. Studies A2336 and A2337 were conducted as part of the combination GP/Ind development program, and each included single-ingredient GP treatment arms as part of the typical factorial design. The single-ingredient GP and corresponding placebo arms from these trials were also included in the GP safety database. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of GP received (12.5 mcg). Safety assessments in these 4 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long term safety study, A2319, was conducted and did not reveal any additional safety signals.

The 3-month safety database included 1,889 COPD patients; 951 treated with GP 12.5 mcg BID and 938 patients treated with placebo. Few patients discontinued from the studies, with more patients discontinuing in the placebo group (88% placebo vs. 92% GP treated patients completed the study). Deaths were infrequent in the clinical development program (n=3 (0.3%), GP vs. n=2 (0.2%) placebo).

The overall occurrence of serious adverse events (SAEs) was low and equally distributed across treatment groups [n=38 (4.1%), placebo vs. n=40 (4.2%) GP]. SAEs that were reported more frequently in the GP group as compared with placebo were infection [n=5 (0.5%) placebo, vs, n=8 (0.8%) GP], neoplasms [n=2 (0.2%), placebo vs. n=4 (0.7%), GP], general and administration site disorders [n=0, placebo vs. n=3 (0.3%) GP], renal and urinary disorders [n=1 (0.1 %), placebo vs. n=2 (0.2 %), GP], vascular disorders [n=0, placebo vs. n=2 (0.2%), GP] and skin disorders [n=0, placebo, n=1 (0.1%), GP]. Overall, SAEs occurred infrequently in the clinical development program, with slight, but clinically insignificant numerical imbalances.

AEs leading to discontinuation were more frequent in the placebo patients (4.1%) compared to (2.5%) in the GP treated patients. COPD-related events such as COPD exacerbations were the most common reason for discontinuation (1.6% placebo vs. 1.0% GP).

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs. The AESIs that occurred more frequently in the GP treated group were the following: bladder outflow obstruction and urinary retention (0.1% placebo, 0.3% GP) and atrial fibrillation/flutter events (0.8% placebo, 1.7% GP). In addition to the AESI, the Applicant conducted a review of major adverse cardiovascular events (MACE) which have been a historical concern with this drug class. MACE events occurred more frequently in the placebo group (0.6%) compared to the GP-treated patients (0.4%).

Patients experiencing at least one adverse event were fairly balanced between the placebo and GP treatment groups (42.5% placebo, 44.2 % GP). Common adverse reactions that occurred in at least 1% in any treatment group and more were more common in the GP treated group included: upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, sinusitis, and urinary tract infection. The findings from the 12-month safety study were consistent with the results seen for the primary 3 month safety database. No new safety signal was identified.

The safety database is adequate to assess the safety of GP. In summary, the safety data for the GP development program in COPD do not reveal any new safety concerns. Adverse events were few and generally those observed with similar approved anti-muscarinic products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data from the 3-month safety database are described here in Section 7. The long-term safety study did not reveal any new safety findings and is discussed when additional data is required for clarification. The protocols for the four studies that comprise the safety database along with the long-term safety study are reviewed in Section 5.

The safety evaluation of GP relies on 3-month data from 4 studies; A2317, A2318, A2336, and A2337. Studies A2336 and A2337 were conducted as part of the combination GP/Ind development program, and each included single-ingredient GP treatment arms as part of the typical factorial design. All analyses in this review were based on the pooled 3-month safety population, unless otherwise specified.

7.1.2 Categorization of Adverse Events

For pooled analyses of studies completed at various times, AEs were re-coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA) (version 17.0) at the time of analysis and any relevant changes that resulted were documented.

AEs were evaluated by primary system organ class (SOC) and by preferred term (PT), and also according to severity (mild, moderate and severe) and according to the investigator's assessment

of the possible relationship to study drug (possibly related or not related). They were classified as common AEs, SAEs including deaths, other significant AEs including AEs causing permanent discontinuation of study treatment or dose interruption, and AEs requiring additional therapy. In addition, AEs of special interest including serious cardiac/cardiovascular (CCV) events adjudicated by MACE outcome and adjudicated atrial fibrillation/flutter were also analyzed.

The analysis of AEs was based on the concept of treatment-emergent AEs. In general, AEs with an onset date (or worsening) between the first intake of study medication and 7 days after the last dose date (respectively 30 days after last dose date for SAEs) were designated as treatment-emergent. Events starting before or after this interval were not included in the analyses of AEs. The assessment of AEs was based on frequencies of patients with AEs rather than exposure adjusted incidence rates.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor utilized multiple safety groupings for the safety analyses of this clinical development program. The sponsor established a primary 3 month safety analysis grouping comprised of the pivotal phase 3 studies (A2317 and A2318) and the GP and placebo arms of the supportive trials (A2336 and A2337); labeled primary 3 month S-db. Analysis of the 3 month safety data is the focus of the safety review.

Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of GP received.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for the 3-month safety database (as defined above) is described in Table 26.

Table 26. Extent of exposure to GP: 3-month pooled safety database		
	GP 12.5 mcg BID N=951	**Placebo N=938**
Duration of exposure (days)		
Mean (SD)	81.7(14.4)	79.1 (18.9)
Total patient-years	212.8	203.1
Duration of exposure categories, n (%)		
≥ 2 weeks	937 (98.5)	915 (97.5)
≥ 4 weeks	922 (97.0)	887 (94.6)
≥ 12 weeks	711 (74.8)	650 (69.3)

Duration of exposure = date of last dose - date of first dose + 1.
SD=standard deviation
Source: Module 2.7.4, Summary of Clinical Safety, Table 1-11, page 39.

As shown in Table 26, the mean duration of exposure was similar across treatment groups, at approximately 80 days. 70% of placebo patients and 75% of GP treated patients were exposed to study drug for ≥ 12 weeks. The extent of exposure in the 3 month safety database was adequate to perform the safety evaluation for GP 12.5 mcg BID in patients with COPD.

Demographics

Demographic information for the pooled 3-month safety database is summarized in Table 27.

Table 27. Demographics- 3-month pooled safety database		
	GP 12.5 mcg BID N=951	**Placebo N=938**
Female n (%)	372 (39.1)	378 (40.3)
Mean BMI kg/m2 (SD)	27.9 (5.4)	27.4 (5.4)
US site n (%)	732 (77.0)	709 (75.6)
Age Categories, n (%)		
Mean age (range)	63.3 (43-87)	63.0 (41-87)
<65 years	528 (55.5)	527 (56.2)
65-<75 years	319 (33.5)	328 (35.0)
≥75 years	104 (10.9)	83 (8.8)
Race, n (%)		
White	848 (89.2)	842 (89.8)
Asian	16 (1.7)	11 (1.2)
Black	55 (5.8)	65 (6.9)

Source: Module 2.7.4, Summary of Clinical Safety, Table 1-18, p47

The mean age of the patient population was 63 years and a larger proportion of the randomized population was male and Caucasian. The demographic parameters were fairly evenly split

between the two treatment groups. Most patients were current smokers with a COPD severity of moderate (GOLD 2) according to the 2011 GOLD guidelines.

Demographics A2319

In Study A2319, the 2 treatment groups (GP12.5 mcg BID and Ind 75 mcg QD) were broadly similar for demographic characteristics. The mean age of patients was 63.3 years, with 12% of the total population being ≥75 years of age. The majority of the patients were male (57.2%) and Caucasian (90.9%), with 7.1% of Black patients. Disease severity was generally comparable between the treatment groups in terms of the GOLD combined assessment (GOLD 2011); 51.5% of patients were classified as Group B with 45% classified as Group D. The median duration of COPD was similar between treatments (5.1 years overall). The percentage of patients using an ICS at baseline was also similar between both treatment groups (36.5% overall). Over half of all patients in the study were current smokers with a similar distribution across the treatment groups between current and former smokers.

7.2.2 Explorations for Dose Response

Explorations for dose response were conducted by the Applicant prior to the conducting the phase 3 program, in which only one dose was investigated.

Two dose ranging studies were conducted during the development program; A2205 and A2208. A2205 investigated once daily doses of 12.5 mcg, 25 mcg, 50 mcg, and 100 mcg in patients with moderate to severe COPD to characterize the dose response for GP. Study A2208 was conducted to assess both QD dosing of 12.5 mcg, 25 mcg, 50 mcg, and 100 mcg and BID dosing of 12.5 mcg, 25 mcg, and 50 mcg, and placebo over 28 days. The efficacy results of the dose-ranging studies which led to dose selection in the phase 3 program are described in Section 5.1 (Table of Clinical Studies) and in 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

(b) (4)

GP 12.5 mcg BID was the lowest twice daily dose which demonstrated statistically significant and clinically meaningful efficacy. Based on these findings the 12.5 mcg dose was selected for the phase 3 program.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required to further explore the safety profile of GP.

7.2.4 Routine Clinical Testing

All laboratory samples were processed through the central laboratory. The routine clinical testing in the development program for GP included: hematology, blood chemistry and urinalysis and ECGs.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

GP is an approved product (NDA # 012827 Robinul Forte 2 mg tablet/ Robinul 1 mg tablet, NDA # 017558 0.2mg/mL injection, NDA # 014764 0.2mg/mL injection, NDA # 012827 1mg tablet, ANDA # 202675 1 mg tablet, ANDA # 091522 1.5 mg tablet, ANDA # 091182 multiple strengths tablet, ANDA # 090963 0.2mg/mL injection, ANDA # 090195 multiple strengths tablet, ANDA # 090020 multiple strengths tablet, NDA # 089397 0.2 mg/mL injection, ANDA # 089393 0.2mg/mL injection, ANDA # 089335 0.2mg/mL injection, ANDA # 088475 0.2mg/mL, ANDA # 086947 0.2mg.mL injection, ANDA # 086902 1mg tablet, ANDA # 086900 2mg tablet, ANDA # 086178 2mg tablet, ANDA # 085563 2mg tablet, ANDA # 085562 1 mg tablet, ANDA # 081169 0.2mg/mL injection, ANDA # 040847 multiple strengths tablet, ANDA # 040844 multiple strengths tablet, ANDA # 040836 multiple strengths tablet, ANDA # 040821 multiple strengths tablet, ANDA # 040653 multiple strengths tablet, ANDA # 040568 multiple strengths tablet, NDA # 022571 Cuvposa 1mg/5mL oral solution) and is therefore not considered a new molecular entity (NME). GP is an anticholinergic and the adverse events that have been identified are common to other drugs in the class. The adverse events associated with anticholinergic agents consist of the following; xerostomia, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, dilatation of the pupil, cycloplegia, increased ocular tension, loss of taste, headaches, nervousness, mental confusion, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, constipation, bloated feeling, impotence, suppression of lactation, severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations.

7.3 Major Safety Results

7.3.1 Deaths

Deaths are summarized in Table 28.

Table 28. Deaths- Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Deaths	3(0.3)	2(0.2)
Cardiovascular	1 (0.1)	2 (0.2)
Fatal MI	0	1 (0.1)
Pump Failure	0	1 (0.1)
Sudden death	1 (0.1)	0
Other	1 (0.1)	0
Infection	1 (0.1)	0
Unknown	1 (0.1)	0

Causes of death were determined by an independent adjudication committee. All deaths were Adjudicated. Only deaths occurring on treatment plus 30 days after end of treatment are included.

Source: Module 2.7.4, Summary of Clinical Safety, Table 2-10, page 86.

The number of deaths was similar in both treatment groups. Overall, death was a rare occurrence in the 3-month pooled safety database and small differences between treatment groups were not clinically significant. Similar results were observed in the long term 12 month safety database described below in Table 29.

Table 29. Deaths- Pooled 12 Month Safety Database

	GP 12.5 mcg BID N=251 n (%)	Ind 75 mcg QD N=256 n (%)
Deaths[a]	2(0.8)[a]	1(0.4)[a]
Cardiovascular	2(0.8)[a]	1 (0.4)[a]
Sudden death - Last seen between 1 and 24 h	1 (0.4)	0
Sudden death - Witnessed within 1 h	1 (0.4)	1 (0.4)

Causes of death were determined by an independent adjudication committee. All deaths were adjudicated. Only deaths occurring on treatment plus 30 days after end of treatment are included.
[a] 2 deaths in the GP 12.5 mcg BID group and 1 death in the Ind 75 mcg QD group were reported more than 30 days after last dose of study medication and are not included in this table

Source: Module 2.7.4, Summary of Clinical Safety, Table 2-11, page 88.

7.3.2 Nonfatal Serious Adverse Events

An overview of serious adverse events (SAEs) is provided in Table 30 .

Table 30. Serious Adverse Events- Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Patients with at least one SAE by SOC	40 (4.2)	38 (4.1)
Respiratory, thoracic and mediastinal disorders	15 (1.6)	19 (2.0)
Chronic obstructive pulmonary disease	14 (1.47)	16 (1.71)
Acute respiratory failure	1 (0.11)	1 (0.11)
Lung infiltration	1 (0.11)	0
Respiratory failure e	1 (0.11)	2 (0.21)
Aspiration	0	0
Hemoptysis	0	2 (0.21)
Pulmonary mass	0	1 (0.11)
Infections and infestations	8 (0.8)	5 (0.5)
Pneumonia	4 (0.42)	1 (0.11)
Cellulitis	1 (0.11)	0
Epiglottitis	1 (0.11)	0
Herpes simplex	1 (0.11)	0
Ophthalmic herpes zoster	1 (0.11)	0
Perirectal abscess	1 (0.11)	0
Upper respiratory tract infection (bacterial)	1 (0.11)	1 (0.11)
Bronchitis	0	1 (0.11)
Influenza	0	1 (0.11)
Lower respiratory tract infection	0	0
Sinusitis	0	1 (0.11)
Urinary tract infection	0	0
Wound infection	0	1 (0.11)
Cardiac disorders	7 (0.7)	7 (0.8)
Acute myocardial infarction	2 (0.21)	1 (0.11)
Atrial fibrillation	2 (0.21)	1 (0.11)
Acute coronary syndrome	1 (0.11)	0
Angina pectoris	1 (0.11)	2 (0.21)
Cardio respiratory arrest	1 (0.11)	0
Cardio pulmonary failure	1 (0.11)	0
Cardiac arrest	0	2 (0.21)
Cardiac failure	0	1 (0.11)
Cardiac failure congestive	0	1 (0.11)
Coronary artery disease	0	2 (0.21)
Myocardial infarction	0	0
Ventricular tachycardia	0	1 (0.11)
Neoplasms benign, malignant and unspecified	4 (0.4)	2 (0.21)
Lung neoplasm malignant	1 (0.11)	0
Metastatic squamous cell carcinoma	1 (0.11)	0
Squamous cell carcinoma of skin	1 (0.11)	0
Squamous cell carcinoma of vulva	1 (0.11)	0

Hepatic cancer	0	1 (0.11)
Prostate cancer	0	1 (0.11)
General disorders and administration site conditions	3 (0.32)	0
Non cardiac chest pain	1 (0.11)	0
Peripheral edema	1 (0.11)	0
Systemic inflammatory response syndrome	1 (0.11)	0
Chest pain	0	0
Renal and urinary disorders	2 (0.21)	1 (0.11)
Renal failure	1 (0.11)	0
Renal failure acute	1 (0.11)	1 (0.11)
Vascular disorders	2 (0.21)	0
Hypertensive crisis	2 (0.21)	0
Peripheral artery aneurysm	1 (0.11)	0
Peripheral ischemia	1 (0.11)	0
Skin and subcutaneous tissue disorders	1 (0.11)	0
Erythema	1 (0.11)	0

SOC= system organ class

Source: Module 2.7.4, Summary of Clinical Safety, Table 2-14, page 94, Appendix 1, table 2.1.3, page 1752

The overall occurrence of SAEs was balanced across treatment groups [n=40 (4.2%) GP, n=38 (4.1%) placebo]. In general, the numbers of patients experiencing individual SAEs were small, without striking imbalances noted. Neoplasms, were more common in the GP group, although this difference was small (n=4 (0.4%) vs. n=2 (0.2%) placebo) and when looking at preferred terms, no clear signal was identified. No new safety signal was noted as a result of the SAE analysis.

7.3.3 Dropouts and/or Discontinuations

Adverse events (AE's) leading to premature treatment discontinuation are listed in Table 31.

Table 31. Adverse Events Leading to Premature Discontinuation occurring in at least 1% in any treatment group - Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Patients ≥1 AE	24 (2.5)	38 (4.1)
COPD	9 (1.0)	15 (1.6)

A patient with multiple adverse events within a preferred term is counted only once for that preferred term.
Only AEs reported while on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

Source: Module 2.7.4, Summary of Clinical Safety, Table 2-17, page 100.

Overall, few patients discontinued treatment prematurely in the GP development program. Discontinuations secondary to adverse events was therefore also infrequent. In fact, more subjects discontinued treatment due to an AE in the placebo group; n=38 (4%) compared to GP (n=24 (2.5%). The most common AE leading to discontinuation was COPD related, such as COPD exacerbations. Overall, adverse events were not a significant cause for patient discontinuation.

7.3.4 Significant Adverse Events

No adjustments to the study drug dosage or schedule were permitted, other than temporarily interrupting study medication during the treatment period as a result of an AE (including COPD exacerbations), if necessary.

AE's leading to dose interruption are listed in Table 32.

Table 32. Adverse Events Requiring Dose Interruption - Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Patients with at least one AE	17 (1.8)	8 (0.9)
Cardiac Disorders	3 (0.3)	1 (0.1)
Acute Coronary Syndrome	1 (0.1)	0
Acute myocardial Infarction	1 (0.1)	0
Tachycardia	1 (0.1)	0
Angina Pectoris	0	0
Coronary artery Disease	0	1 (0.1)
Ear and Labyrinth Disorders	1 (0.1)	0
Vertigo	1 (0.1)	0
Gastrointestinal Disorders	1 (0.1)	1 (0.1)
Inguinal Hernia	1 (0.1)	0
Nausea	0	1 (0.1)
Infections and Infestations	4 (0.4)	2 (0.2)
Bronchitis	1 (0.1)	0
Cellulitis	1 (0.1)	0
Herpes Simplex	1 (0.1)	0
Opthalmic Herpes Zoster	1 (0.1)	0
Pneumonia	1 (0.1)	0
Upper Respiratory Tract Infection (bacterial)	1 (0.1)	0
Gastroenteritis (Viral)	0	2 (0.2)
Injury, Poising and Procedural Complications	2 (0.2)	0
Femur Fracture	1 (0.1)	0
Heat Stroke	1 (0.1)	0
Investigations	1 (0.1)	0

Volume Blood Decreased	0	1 (0.1)
Nervous System Disorders	1 (0.1)	1 (0.1)
Convulsion	1 (0.1)	0
Headache	0	1 (0.1)
Renal and Urinary Disorders	1 (0.1)	0
Renal Failure Acute	1 (0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	8 (0.8)	4 (0.4)
Chronic Obstructive Pulmonary Disease	8 (0.8)	3 (0.3)
Acute Respiratory Failure	1 (0.1)	0
Pleuritic Pain	0	1 (0.1)
Skin and Subcutaneous Tissue	1 (0.1)	0
Rash	1 (0.1)	0

System organ classes are presented in alphabetical order; preferred terms are sorted within system organ class in descending order of percentages in the NVA 12.5 bid group. A patient with multiple AEs is counted only once in the "at least one AE" row. A patient with multiple AEs within a system organ class is counted only once in that system organ class row. A patient with multiple AEs with the same preferred term is counted only once for that preferred term. Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

Source: Module 2.7.4, Summary of Clinical Safety, Appendix 1, Table 2.1.4, p1996

The overall incidence of AEs leading to dose interruption was low, with a higher rate in the GP group (1.8%) compared to the placebo group (0.9%). The most commonly affected SOC was respiratory, thoracic and mediastinal disorders [GP: n=8 (0.84%), placebo: n=4 (0.43%)), primarily due to COPD (GP 0.8%, placebo 0.3%]. All other AEs in both treatment groups were singular in nature (reported in 1 patient each) except for gastroenteritis viral, which required dose interruption for 2 patients in the placebo group and none in the GP group.

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest included adjudicated major adverse cardiovascular events (MACE), adjudicated atrial fibrillation/flutter, sudden death, adverse effects compatible with an anticholinergic mechanism of action, and respiratory events including paradoxical bronchospasm.

<u>Cardiovascular and cerebrovascular events adjudicated as MACE</u>

Serious cardiovascular or cerebrovascular (CCV) events atrial fibrillation/flutter and deaths were adjudicated by an independent, external, blinded, adjudication committee to determine whether they fulfilled criteria for MACE. MACE events were categorized as follows: a) Non-Fatal Myocardial infarction (MI) b) Unstable angina c) Non-fatal stroke d) Heart failure requiring hospitalization e) Coronary revascularization (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]). If a serious CCV event did not meet the MACE criteria, it was adjudicated, but as a non-MACE event. The adjudicated MACE definition described above was also expanded to include cardiovascular death and is called "MACE and/or Cardiovascular Death". These events are shown in Table 33.

Table 33. Cardiovascular and cerebrovascular events adjudicated as MACE - Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Adjudicated MACE or Cardiovascular Death	5 (0.5)	6 (0.6)
Adjudicated MACE	4 (0.4)	6 (0.6)
Non-Fatal Myocardial Infarction (MI)	4 (0.4)	2 (0.2)*^
Non-Fatal Unstable Angina	0	0
Non-Fatal Stroke	0	1 (0.1)
Heart Failure (HF) Requiring Hospitalization	0	1 (0.1)^
Coronary Revascularization (CABG or PCI)	0	3 (0.3)*
Cardiovascular Death	1 (0.1)°	2 (0.2)°

* patients with both non-fatal MI and coronary revascularization
^ 1 patient with non-fatal MACE event subsequently died due to CV cause
Cardiovascular death was reported for: 1 NVA237 patient and 2 placebo patients
Note the listed terms for AEs of special interest are pooled terms which may include more than one associated preferred term.
Classification for MACE and atrial fibrillation/flutter was determined by an independent adjudication committee.
Events starting on or after the time of first administration of study drug but not later than 30 days after the last administration are included

Source: Module 2.7.4, Summary of Clinical Safety, Table 1-0, page 18.

Overall, adjudicated MACE and/or cardiovascular death rates occurred infrequently in the GP development program, and were slightly lower in the GP (0.5%) compared to placebo (0.6%) groups. Overall, MACE events were infrequent and generally balanced between the two groups.

Serious Cardiovascular and Cerebrovascular Events: Atrial fibrillation/ Atrial flutter

Atrial fibrillation and atrial flutter events (either reported as an AE or detected by centralized ECG finding) were adjudicated by the same independent committee that adjudicated deaths and serious CCV events. They were categorized as new onset, recurrent/persistent, or unknown. These events are listed in Table 34.

Table 34. Serious Cardiovascular and Cerebrovascular Events - Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
CCV events: Any category	16 (1.7)	14 (1.5)
Patients with at least one adjudicated serious CCV AE	8 (0.8)	8 (0.9)
Non-MACE serious CCV AE	4 (0.4)	5 (0.5)
Any atrial fibrillation/flutter event	16 (1.7)#	7 (0.8)

New onset	5 (0.5)	1 (0.1)
Recurrent/persistent	12 (1.3)	6 (0.6)
Unknown	0	0
Any atrial fibrillation event	15 (1.58)	7 (0.75)
New onset	3 (0.32)	1 (0.11)
Recurrent/persistent	12 (1.26)	6 (0.64)
Unknown	0	0
Any atrial fibrillation/flutter event	2 (0.21)	0
New onset	2 (0.21)	0
Recurrent/persistent	0	0
Unknown	0	0

One patient had both recurrent/persistent atrial fibrillation and new onset atrial flutter. Hence counted once in the total category

Note the listed terms for AEs of special interest are pooled terms which may include more than one associated preferred term.
Classification for MACE and atrial fibrillation/flutter was determined by an independent adjudication committee.
Events starting on or after the time of first administration of study drug but not later than 30 days after the last administration are included
Only the first occurrence of an event during treatment is counted for the category of onset.

Source: Module 2.7.4, Summary of Clinical Safety, Table 1-0, page 18. Table 2-25, p115, Table 2-23, p126

Adjudicated atrial fibrillation/atrial flutter events occurred infrequently and are summarized in Table 34. There was a small numerical imbalance of "increase in atrial fibrillation/flutter" events in the GP group (1.7%) compared to the placebo group (0.8%) as well as both "new onset atrial fibrillation/flutter "(0.5% vs. 0.1%) and "recurrent/persistent atrial fibrillation/flutter" (1.3% vs. 0.6%). Most of the atrial fibrillation/flutter events were classified as atrial fibrillation [GP n=15 (1.6%), Placebo n=7 (0.8%)]. The new onset events were considered SAEs for two of the GP patients and 1 of the placebo patients. None of the patients with adjudicated new onset atrial fibrillation/flutter had adjudicated MACE events and all of these patients (with the exception of 2) had at least one CV risk factor at baseline.

Review of the 12 month safety data provided some reassurance that these events balance out over time. The occurrence of any atrial fibrillation/flutter events occurred slightly more frequently in the Ind 75 mcg QD group compared to the GP group [GP n=4 (1.6%), Ind n=5 (2%)]. This was also demonstrated for new onset atrial fibrillation/flutter events [GP n=1 (0.4%), Ind n=2 (0.8%)]. However, recurrent/persistent events still occurred more frequently in the GP group [GP n=4 (1.6%), Ind n=1 (0.4%)].

Overall, the number of events was small, the occurrence of these events did not result in an increase of MACE events in the GP group and the events appear to balance out across the treatment groups over time. The numerical imbalances identified with atrial fibrillation/flutter were small and of unclear clinical significance.

Paradoxical bronchospasm/Anticholinergic Adverse Events

Table 35. Paradoxical bronchospasm/Anticholinergic Adverse Events - Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Paradoxical bronchospasm	5 (0.5)	5 (0.5)
Bladder outflow obstruction and urinary retention	3 (0.3)	1 (0.1)
Narrow angle glaucoma	0	2 (0.2)

Note the listed terms for AEs of special interest are pooled terms which may include more than one associated preferred term.
Only AEs reported whilst on study drug or within 7 days of the last dose (within 30 days for SAEs) are included

Source: Module 2.7.4, Summary of Clinical Safety, Table 1-0, page 18

As can be seen in Table 35, paradoxical bronchospasm was a rare event and balanced between both the placebo and GP groups. Events generally associated with anticholinergic effects were also reported at a low incidence and generally balanced between both the treatment groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 36. Common Adverse Events (occurring in at least 1% in any treatment group) – Pooled 3 Month Safety Database

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Patients with at least 1 AE	420 (44)	399 (42.5)
COPD exacerbation	157 (16.5)	177 (18.9)
Upper respiratory tract infection	32 (3.7)	22 (2.4)
Oropharyngeal pain	23 (2.5)	11 (1.2)
Nasopharyngitis	20 (2.1)	18 (1.9)
Sinusitis	13 (1.4)	7 (0.8)
Urinary tract infection	13 (1.4)	12 (1.3)
Dyspnea	4 (0.4)	16 (1.7)

A patient with multiple adverse events within a preferred term is counted only once for that preferred term.
Only AEs reported while on study drug or within 7 days of the last dose (within 30 days for SAEs) are included.

Source: Module 2.7.4, Summary of Clinical Safety, Table 2-2, page 70.

As shown in Table 36, common adverse events were generally balanced between the GP and placebo groups. The most frequent AE by preferred term was COPD (exacerbation), which was lower in GP compared to placebo. Observed AEs were typical of what is seen in COPD lung function studies and do not raise concern for any new safety signals.

7.4.2 Laboratory Findings

Overall, review of the clinical laboratory data did not reveal any clinically significant differences.

7.4.3 Vital Signs

Vital sign data included systolic blood pressure, diastolic blood pressure, pulse rate, and body weight. There were no clinically significant differences noted.

7.4.4 Electrocardiograms (ECGs)

ECGs were centrally read and reviewed by cardiologists at [redacted] (b) (4), including quantitative and qualitative assessments.

Table 37. Qualitative ECG diagnoses: Number and percentage of patients with newly occurring ECG abnormalities at any time post-baseline by evaluation type

	GP 12.5 mcg BID N=951 n (%)	Placebo N=938 n (%)
Conduction	108 (11.4)	96 (10.2)
Ectopy	76 (8)	58 (6.2)
Morphology	12 (1.3)	11 (1.2)
Myocardial infarction	1 (0.1)*	0
Rhythm	53 (5.6)	37 (3.9)
ST segment	48 (5.0)	51 (5.4)
T waves	113 (11.9)	120 (12.8)
U waves	0	1 (0.1)

A patient is only counted once for each abnormality/evaluation type.
Post-baseline values at all scheduled and unscheduled measurements or premature discontinuation visits up to 7 days after last dose within the respective database are included.
* The patient had myocardial infarction which was an adjudicated MACE event

Source: Module 2.7.4, Summary of Clinical Safety, Table 4-6, page 158.

The number and percentage of patients with newly occurring ECG abnormalities at any time post-baseline are summarized by evaluation type in Table 37. Slight imbalances were noted, with a higher frequency of newly occurring ECG abnormalities in the GP group compared to placebo for ectopy (GP 8.0%, placebo 6.2%) and rhythm (GP 5.6%, placebo 3.9%). For ectopy, the imbalance was mainly driven by a higher proportion of patients with newly occurring atrial premature complexes in the GP group (4.3%) compared to placebo (2.8%). For rhythm, there was a higher proportion of patients in the GP than in the placebo group with newly occurring atrial fibrillation [GP n=3 (0.3%) vs. placebo n=0 (0%)] or atrial flutter [GP n=2 (0.2%) vs.

placebo n=0 patients (0%)]. Differences between treatment groups were generally small and not considered clinically relevant with no patient withdrawing from the study due to ECG abnormalities.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies conducted as part of this NDA.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this small molecule drug product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Refer to section 7.2.2 Explorations for Dose Response.

7.5.2 Time Dependency for Adverse Events

The Sponsor did not comment on a time dependent relationship for adverse events. This is further supported by a similar safety profile in the primary 3 month safety database and the 12 month safety database.

7.5.3 Drug-Demographic Interactions

AEs were evaluated in demographic subgroups (age, sex, and race), by baseline characteristics (COPD severity, CV history/condition and CCV risk factors), by presence of atrial fibrillation/flutter history, and by presence of cardiac arrhythmia history.

In general, AEs by subgroup reflected the pattern seen for the whole population, with most subgroups (where there were sufficient patients) similar to the total database population. The majority of patients (90%) were Caucasian; the subgroups of Black, Asian, and Other patients were too small to show any meaningful trends. Too few events were reported for most categories of AESI to show meaningful results by subgroup. For those categories of AESIs which were reported by more than a few patients, subgroups (of sufficient patients) reflected the pattern seen for the whole population.

7.5.4 Drug-Disease Interactions

Following inhalation of single and repeated once daily doses between 50 and 200 mcg GP by healthy subjects and patients with COPD, the mean amounts of glycopyrronium excreted into the urine varied between 7.7% and 20.0% of the dose, depending on the time interval

considered (up to 24, 48, 72 or 96 h). Mean renal clearance (CLr) of glycopyrronium following inhalation was in the range of 17.4 and 24.4 L/h, including data for healthy subjects (after single dose) and patients with COPD (both after single and repeated dosing).

A population pharmacokinetic analysis identified body weight and age as intrinsic physiological factors contributing to inter-patient variability in systemic exposure to glycopyrronium. The dependence of apparent total body clearance (CL/F) on age was explained by a decrease in eGFR with age in the population studied. Systemic exposure to glycopyrronium increases with increasing patient age: Compared to a 60-year-old subject, average exposure (or AUCtau) was predicted to increase by 37% in an 85-year-old subject and to decrease by 18% in a 40-year old-subject. Systemic exposure to glycopyrronium decreases with increasing patient body weight: Compared to a subject of 74 kg, average exposure was predicted to increase by 47% in a subject of 45 kg, and to decrease by 31% in a subject of 120 kg. Considering the limited magnitude of body-weight and age effects, it was concluded that COPD patients can be dosed with GP 12.5 mcg BID irrespective of body weight and age.

Gender, smoking status, and baseline FEV1 had no relevant effect on maximal or average glycopyrronium systemic exposure.

Based on the pooled PK data used for the PopPK analysis [PopPK GP 12.5 mcg BID] which included 38 patients of Hispanic/Latino ethnicity and 27 patients of Japanese ethnicity, no dependence of the apparent total clearance on ethnicity was detected. Therefore the AUC values at the same dose level were similar between these populations. However peak concentrations were 19% higher in Japanese patients compared to other ethnicities because of a smaller volume of distribution of the central compartment. In conclusion, the PopPK analysis did not reveal a clinically relevant ethnic effect on the systemic exposure to glycopyrronium. The analysis of the single dose and steady-state systemic exposure data following inhalation of GP 50 mcg QD does not indicate a clinically relevant ethnic difference across Chinese subjects, COPD Caucasian patients, healthy Caucasian and Japanese subjects, and between Chinese and non-Chinese subjects.

7.5.5 Drug-Drug Interactions

In vitro studies showed that GP 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 GP and multiple enzymes are involved. Inhibition or induction of metabolism of GP is unlikely to result in a relevant change of GP exposure.

Drug-drug interaction studies were conducted at higher doses than GP 12.5 mcg. The conclusions based on the in vivo interaction studies conducted with higher doses than the proposed 12.5 mcg BID dose can be extrapolated downwards.

<u>Drug interaction with cimetidine</u>

Study A2109 was designed to characterize the effect of inhibition of the organic cation transport on glycopyrronium disposition after GP inhalation using cimetidine as a probe inhibitor of the involved transporters (Dumitras et al 2013). A single inhaled dose of GP 100 mcg was administered to healthy volunteers alone and concomitantly with cimetidine on the fourth day of a 6-day treatment period with cimetidine 800 mg BID, i.e. under pharmacokinetic steady-state conditions of cimetidine. Cimetidine increased total exposure (AUClast) to GP by 22% and this increase correlated with the observed 23% decrease in renal clearance (CLr) of GP upon coadministration of the two drugs. Based on the magnitude of the pharmacokinetic changes seen in this study, no relevant drug interaction is expected when GP is co-administered with cimetidine.

Drug interaction with indacaterol

The sponsor has also submitted an NDA for a combination product with Indacaterol and therefore it is important to evaluate the possibility of a drug interaction with the other monoproduct.

In Study (A2107) the steady-state systemic exposure (AUC0-12h,ss; Cmax,ss) to indacaterol and glycopyrronium was similar after administration in BID fixed-dose combination (FDC) as GPI 27.5/12.5 mcg (x 2) as compared to the BID. administration of indacaterol 27.5 mcg (x 2) alone or GP 12.5 µg (x 2) alone, respectively. Although this study was not designed to be a bioequivalence trial, the upper and lower limit of the 90% CIs for the geometric mean ratio met criteria typically set forth for bioequivalence (BE) trials (80 to 125%).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

GP has been tested *in vitro* and *in vivo* in a complete range of repeated-dose toxicity, genotoxicity, reproductive toxicity and carcinogenicity studies. Repeated-dose inhalation toxicity studies were conducted in rodents and non-rodents for up to nine months. GP was generally well tolerated and no limiting toxicities for use in humans were identified.

No special safety concerns arose from non-clinical safety data obtained with GP that needed to be considered in the clinical evaluation of safety.

7.6.2 Human Reproduction and Pregnancy Data

No clinical data on exposed pregnancies in COPD patients are available. GP was not

teratogenic in rats or rabbits following inhalation administration. Glycopyrronium and its metabolites did not penetrate the brain of mice, rats or dogs and did not cross the placental barrier of pregnant animals and humans to a substantial degree. In human parturients undergoing Caesarean section, 86 minutes after a single intramuscular injection of 0.006 mg/kg glycopyrronium, umbilical plasma concentrations were low and clinically insignificant (Ali-Melkkilä et al 1990). As there are no adequate and well-controlled studies in pregnant women, it is recommended to use GP only during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

N/A in COPD.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

GP is provided as 12.5 mcg inhalation powder hard capsules for oral inhalation. Absolute bioavailability of orally inhaled GP was estimated to be about 40%, and absolute oral bioavailability of GP to be about 5%. Therefore, if a patient accidentally or intentionally ingests and swallows an inhalation capsule, the systemic bioavailability is expected to be about 8-fold lower than that after oral inhalation from an inhalation capsule. Due to the low oral bioavailability, a patient would have to swallow approximately 130 capsules to achieve a systemic exposure similar to that following oral inhalation of a 200 mcg dose.

In addition, GP has been in clinical use for many years as tablets (Robinul tablets) at doses up to 6 mg daily (Robinul and Robinul forte Prescribing Information 2010), corresponding to 4.8 mg active moiety (i.e. glycopyrronium). A daily dose of 4.8 mg active moiety (glycopyrronium) corresponds to the GP content of 384 inhalation capsules. Therefore, acute intoxication by inadvertent oral ingestion of GP capsules is highly unlikely.

In the unlikely event of an overdose of GP; anticholinergic signs and symptoms such as nausea, vomiting, dizziness, lightheadeness, blurred vision, increased intraocular pressure (causing pain, vision disturbances or reddening of the eye), obstipation or difficulties in voiding may occur.

7.7 Additional Submissions / Safety Issues

7.7.1 120 Day Safety Update

The updated safety information provided in the 120-Day update is from GP 50 mcg QD and includes ongoing and completed studies between September 29, 2014 and December 31, 2014. There were no ongoing studies for the GP 12.5 mcg BID dose. The update includes information from 2 completed studies (NVA237AAU01a and NVA237AAU02). Study NVA237AAU01

assessed the efficacy, tolerability and safety of GP (50 mcg QD) compared to tiotropium (Tio; 18 mcg QD) and placebo, all three added on to fluticasone/salmeterol (Flu/Sal; 500/50 mcg BID) in patients with chronic obstructive pulmonary disease. While study NVA237AAU02 assessed the early bronchodilation of GP (50 mcg QD) compared to Tio (18 mcg. QD) in patients with moderate to severe COPD. In addition, safety data from numerous ongoing studies were submitted as part of this update. The studies included post marketing studies, including a 4 ½ year, multinational, open label cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled GP in Europe.

Overall, the type and frequencies of events reported in this 4-month Safety Update were consistent with those reported at the time of the original data base lock for the SCS and therefore confirmed a similar safety profile for GP dosing.

7.7.2 Long Term Safety

The findings from the 12 month safety study were consistent with the results seen for the primary 3 month safety database. No new safety signal was identified. Results of the long-term safety trial are embedded within the 3-month safety database review.

8 Postmarket Experience

Four Periodic Safety Update Reports (PSURs) on Seebri® Breezhaler® and related products (glycopyrronium bromide 50 mcg QD) have been prepared thus far, covering the reporting intervals from Sep 29, 2012 to Mar 28, 2013 (PSUR 1), from Mar 29, 2013 to Sep 28, 2013 (PSUR 2), from Sep 29, 2013 to Mar 28, 2014 (PSUR 3) and from Mar 29, 2014 to Sep 28, 2014 (PSUR 4) respectively. The estimated cumulative post-marketing exposure to Seebri® Breezhaler® is 339,914 PTY.

A critical analysis of the post-marketing safety data received during the first four PSUR periods revealed few new safety topics.

Hypersensitivity – (generally known as an ADR associated with inhaled antimuscarinic medicinal compounds (e.g., tiotropium)) - emerged as a new finding based on several postmarketing reports of various manifestations of hypersensitivity events which consisted of angioedema-like reactions or angioedema, skin reactions, pruritus or hypersensitivity. Based on the cases received, hypersensitivity is included in the Contraindication, Warning&Precaution as well as to the ADR section of the proposed United States prescribing information (USPI). In the majority of cases, the episodes were of mild severity (non-serious AEs) and resolved under continued study medication [PSUR 4-Section 16.2.2].

Paradoxical bronchospasm is identified as an ADR in the post-marketing section based on two well documented, not confounded events from spontaneous reports through post-marketing surveillance of the NVA237 50 µg o.d. dose, which is the approved dose in Europe and rest ofm the world

Two ongoing epidemiological studies are currently investigating real world use of glycopyrronium 50 mcg QD treatment. The second interim report of study CNVA237A2401T shows that prescribing patterns are in keeping with the prescribing information. In the second study, CNVA237A2402T, the second interim report does not include sufficient patients to allow for meaningful conclusions at this time.

In conclusion, the review of all newly received safety reports from post-marketing sources did not reveal any additional new safety signal for Seebri® - beyond those mentioned above – that warranted additional actions.

9 Appendices

9.1 Literature Review/References

1. NDA 21936, Medical Review by Dr. Robert Lim
   http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/021936Orig1s000MedR.pdf

2. Robert A. Wise. Tiotropium Respimat Inhaler and the Risk of Death in COPD. NEJM October 17, 2013 vol. 369 no. 16

9.2 Labeling Recommendations

Suggested Revisions to Proposed Labeling

While the labeling has not been finalized at the time this review is being completed, we have proposed the following general recommendations as summarized below.

Section 6 Adverse Reactions: Immediate hypersensitivity reactions added

Section 14.1 Dose Ranging Trials: Inclusion of dose ranging curves for all studied doses in study A2208 on Day 1 and Day 85.

Section 14.2 Confirmatory Trials: Remove [redacted] (b) (4). Information will be included with less granularity in paragraph form. SGRQ should be included and reflect responder analysis for individual studies [redacted] (b) (4). Remove the [redacted] (b) (4) claim as this is a chronically administered drug. Include a brief description of the supportive studies A2336 and A2337.

9.3 Advisory Committee Meeting

The risk-benefit assessment of the use of anticholinergic medications in the treatment of COPD is well-established; further, GP is not a NME. Therefore, an advisory committee was neither convened, nor required, for this application.

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

/s/

ERIKA N TORJUSEN
09/24/2015

BANU A KARIMI SHAH
09/24/2015

MEDICAL OFFICER FILING REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 207923	**TRADE NAME:**	NVA237
APPLICANT/SPONSOR:	Novartis	**USAN NAME:**	SEEBRI NEOHALER
MEDICAL OFFICER:	Erika Torjusen, M.D., MHS		
TEAM LEADER:	Banu Karimi Shah, M.D.	**CATEGORY:**	Glycopyrrolate
DATE:	02/27/2015	**ROUTE:**	Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
12/29/14	12/29/14	NDA 207923	Original NDA

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

Novartis has submitted a 505(b)(1) application for glycopyrronium (GP) 12.5 mcg inhalation via the neohaler BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

The key studies in the clinical development program include; 2 phase 3 trials comparing GP 12.5 mcg inhalation BID vs. placebo evaluating FEV1 AUC (0-12h) at week 12 as the primary endpoint, 1 long term safety study (52 weeks) comparing GP 12.5 mcg BID to Indacaterol (Ind) 75mcg QD and 1 dose ranging study evaluating 12.5, 25, 50 and 100 mcg QD/BID doses of GP. Numerous supportive studies have also been submitted and are outlined in the body of this review.

The submission is fileable. There are no filing comments for the Sponsor.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILEABLE**___X___	**NOT FILEABLE**_____	
	APPROVAL_____	**APPROVABLE**_____	**NOT APPROVABLE**_____
OTHER ACTION:	**COMMENTS FOR SPONSOR**_____		

1. General Information

Novartis has submitted a 505(b)(1) application for glycopyrronium (GP) 12.5 mcg inhalation via the neohaler BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

2. Regulatory History

Prior to submission of this NDA, this product has been the subject of multiple regulatory proceedings. The key regulatory interactions are summarized below. Because this product has been simultaneously developed as a combination product with Indacaterol, some of the regulatory history involves the combination product.

Table 1. Key Regulatory History

Interaction	Date	Highlights
EOP2	7/2008	Explore dose ranging /dosing regimens Evaluate spirometry at multiple time points in P3
Type A SPA	5/2009	"No Agreement" letter issued Further evaluation of dose/interval required
Type A Post-SPA	7/2009	Explore lower doses/alternative regimens out to 28 days Serial spirometry at 14 and 28 days
EOP2a	1/2010	Evaluate more frequent dosing intervals (TID/QID) Consider ipratropium AC- dose frequency determinations (b) (4) Serial spirometry at 1, 14 and 28 days
Pre NDA	9/2011	(b) (4) Explore more frequent/lower doses (b) (4)
EOP2 f/u*	3/2012	(b) (4) risk profile unacceptable for approval (b) (4) 28 day dose ranging studies (b) (4)
Pre NDA*	3/2014	Small US population in clinical program
*Meetings for combination product		

3. Marketing History

(b) (4)

4. Items Required for Filing

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h): 1.1.2
- Index : eCTD
- Summary 2.7 (clinical summary)
- Clinical study reports
    - Study reports 5.3.5.1
    - Reports of analyses of data from more than one study: 5.3.5.3
    - Integrated summary of efficacy 5.3.5.3.27
    - Integrated summary of safety 5.3.5.3.28
    - Good Clinical Practice: within the body of each CSR
    - Debarment certification: 1.3.3
    - Pediatric use: 1.9.1- Waiver
- Labeling: 1.14
- Case report forms: 5.3.5.1
- Financial disclosure 1.3.4

5. Development Program

The key studies in the clinical development program include; 2 phase 3 trials comparing GP 12.5 mcg inhalation BID vs. placebo evaluating FEV1 AUC (0-12h) at week 12 as the primary endpoint, 1 long term safety study comparing GP 12.5 mcg BID to Indacaterol (Ind) 75mcg QD and 1 dose ranging study evaluating 12.5, 25, 50 and 100 mcg QD/BID doses of GP. Numerous supportive studies have also been submitted and are outlined in the body of this review.

Table 2. Key Studies

Study	Design	Duration	N	Treatment	1° Endpoint
NVA237 (GP)					
A2208	R, DB, PC, MC, 2 Period CO	28 days	388	GP 12.5 mcg QD/BID GP 25mcg QD/BID GP 50mcg QD/BID GP 100mcg QD/BID	mean trough FEV1 (12.5QD/25 QD)
A2317	R, DB, PC, MC	12 wks	441	GP 12.5 mcg BID Pbo	FEV1 AUC (0-12h) @wk 12
A2318	R, DB, PC, MC	12 wks	432	12.5 mcg BID Pbo	FEV1 AUC (0-12h) @wk 12
A2319	R, DB, PG, AC, MC	52 wk	511	GP 12.5 mcg BID Ind 75mcg QD	AE's
R=randomized, DB=double-blind, PC=placebo controlled, MC=multi center, CO=cross over, AC= active control, Pbo=placebo					

Table 3. P1/2 Studies

Study	Design	Duration	N	Treatment
A2206	R, DB, PG, PC, AC, MC	28 days	281	GP 100mcg QD GP 200mcg QD Pbo
A2207	R, DB, PG, PC, CO, MC	14 days	33	GP 50mcg QD Pbo
A2303	R, DB, PC, PG, MC, OL-Tio	52 wks	1060	GP 50mcg QD Tio 18mcg QD Pbo
A2304	R, DB, PC, PG, MC	26 wks	817	GP 50mcg QD Pbo

A2205	R, DB, PC, CO, MC	7 days	83	GP 12.5mcg QD GP 25mcg QD GP 50mcg QD GP100mcg QD Placebo Tiotropium 18mcg QD
A2309	R, DB, PC, PG, MC	26 wks	459	GP 50mcg QD Pbo
R=randomized, DB=double-blind, PC=placebo controlled, MC=multi center, CO=cross over, AC= active control, Pbo=placebo, OL=open label				

Table 4. Additional P1/2 Studies

Study	Design	Duration	N	Treatment
A2310	R, DB, PC, CO, MC	21 days	108	GP 50mcg QD Pbo
A2314	R, B, DD, PG, PC, AC, MC	12 wks	657	GP 50mcg QD Tio 18mcg QD Pbo
A2316	R, DB, PG, PC, MC	12 wks	447	GPI 50/150mcg QD GP 50mcg + Pbo
A1302	R, MC, PG, OL	52 wks	163	GP 50mcg QD Tio 18mcg QD
A1301*	R, MC, B, CO	2 x 28 days	126	GP 50mcg +Pbo QD Tio 18mcg + Pbo QD
AU01	R, B, AC, PG	12 wks	785	GP 50mcg +Flut/Salm 500/50 QD Tio 18mcg + Flut/Salm 500/50 QD Flut/Salm 500/50 BID
ACH01	R, DB, MC	2x 1day	79	GP 50mcg + Ind 150mcg QD Ind 150mcg + Pbo
ADE02	R, DB, MC, CO	2x 1day	152	GP 50mcg + Pbo QD Tio 18mcg +Pbo QD
*ongoing R=randomized, DB=double-blind, PC=placebo controlled, MC=multi center, CO=cross over, AC= active control, Pbo=placebo, OL=open label				

Summary of Efficacy and Safety in the Pivotal and Supportive Phase III trials

Efficacy

The clinical development program for GP 12.5 mcg included two similar 12-week, randomized, double-blind, placebo-controlled, parallel-group trials in subjects with COPD designed to evaluate the efficacy of GP 12.5 mcg on lung function. The 12-week trials treated 867 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a post-bronchodilator FEV1 greater than or equal to 30% and less than 80% of predicted normal values, had a ratio of FEV1/FVC of less than 0.7, and were symptomatic as determined by a Modified Medical Research Council (mMRC) score greater than or equal to 2. Of the 867 subjects included in the efficacy analysis, 58% were male and 89% were Caucasian. They had a mean age of 63 years and an average smoking history of 53 pack-years, with 57% identified as current smokers, and 29% using inhaled corticosteroids. At screening, the mean post-bronchodilator percent predicted FEV1 was 55% (range: 30% to 83%), the mean post-bronchodilator percent FEV1/FVC was 51% (range: 24% to 69%), and the mean percent reversibility was 20% (0% to 169%).

Trials A2317 and A2318 evaluated GP 12.5 mcg twice-daily and placebo twice-daily. The primary endpoint was the change from baseline in FEV1 AUC0-12h following the morning dose at Day 85 (defined as the mean FEV1 change from baseline over 0 to 12 hours divided by 12 hours) compared with placebo. The high level results per the sponsor's analysis are shown below Table 5).

Table 5. Primary Efficacy Endpoint for Pivotal P3 Trials

Improvement of Airflow Obstruction (FEV1 AUC (0-12h) at Week 12) – Study A2317, Study A2318

Variable	Statistic	Treatment difference (NVA237–placebo) in change from baseline for FEV_1 (L) $AUC_{(0-12h)}$ at Week 12	
		Study A2317	Study A2318
Change from baseline for FEV_1 (L) $AUC_{(0-12h)}$	LS Mean	0.139	0.123
	95% CI	0.095, 0.184	0.081, 0.165
	p-value	<0.001	<0.001

Safety

Per the Sponsor's analysis, the AEs reported in the studies were consistent with those expected in a COPD population with typically associated co-morbidities. The number of AEs suspected to be drug related was low and there was no clinically relevant difference between the treatment groups.

Table 6. Summary of AEs for the Safety Population

	3mo		12mo	
	GP 12.5 mcg BID N (%)	Placebo N(%)	GP 12.5 mcg BID N (%)	Ind 75mcg QD
Total treated	951	938	251	256
At least 1 AE	420 (44.2)	399 (42.5)	194 (77.3)	197 (77.0)
AE leading to DC	24 (2.5)	38 (4.1)	22 (8.8)	25 (9.8)
At least 1 SAE	40 (4.2)	38 (4.1)	33 (13.1)	34 (13.3)
Deaths	3 (0.3)	2 (0.2)	2 (0.8)	1 (0.4)

Deaths: 8
GP: 2 sudden death/cardiopulmonary failure, infection, and unknown
PBO: MI-cardiac arrest and CHF
IND: sudden death

Table 7. Adverse Reactions (GP) Greater ≥1% Incidence and Higher than Placebo

Adverse Reaction	SEEBRI NEOHALER 15.6 mcg b.i.d. (N=951) n (%)	Placebo (N=938) n (%)
Infections and infestations		
Upper respiratory tract infection	32 (3.4)	22 (2.3)
Nasopharyngitis	20 (2.1)	18 (1.9)
Urinary tract infection	13 (1.4)	12 (1.3)
Sinusitis	13 (1.4)	7 (0.7)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	17 (1.8)	11 (1.2)

Table 8. MACE Primary Safety Database

Adjudicated MACE outcome	3-month		12-month	
	NVA237 12.5 (b.i.d.) n (%)	Placebo n (%)	NVA237 12.5 (b.i.d.) n (%)	QAB149 75 (o.d.) n (%)
Total Treated	951	938	251	256
MACE and/or cardiovascular death	5 (0.5)	6 (0.6)	6 (2.4)	5 (2.0)
MACE	4 (0.4)	6 (0.6)	4 (1.6)	5 (2.0)
Non-Fatal Myocardial Infarction	4 (0.4)	2 (0.2)[a,b]	2 (0.8)[e]	3 (1.2)[c]
Non-Fatal Unstable Angina	0	0	0	0
Non-Fatal Stroke	0	1 (0.1)	0	0
Heart Failure Requiring Hospitalization	0	1 (0.1)	0	0
Coronary Revascularization (CABG or PCI)	0	3 (0.3)[a]	4 (1.6)	3 (1.2)[d]
Cardiovascular death	1 (0.1)	2 (0.2)	2 (0.8)	1 (0.4)[c]

Table 9. Primary Efficacy Endpoint
Improvement of Airflow Obstruction (FEV1 AUC(0-12h) at Week 12) – Studies A2317, A2318

Variable	Statistic	Treatment difference (NVA237–placebo) in change from baseline for FEV_1 (L) $AUC_{(0-12h)}$ at Week 12	
		Study A2317	Study A2318
Change from baseline for FEV_1 (L) $AUC_{(0-12h)}$	LS Mean	0.139	0.123
	95% CI	0.095, 0.184	0.081, 0.165
	p-value	<0.001	<0.001

6. Brief Review of Proposed Labeling

The label is submitted in PLR format. High level review of the label reveals that secondary endpoints are presented in pooled and tabular format. These will likely be excluded from the label. Recently approved products such as; Umeclidinium (Incruse), Umeclidinium/VilanterolI (Anoro) and Indacaterol (Arcapta Neohaler) will be used as labeling guides.

7. DSI/Audit

The clinical team will work with the statistical reviewers to determine which sites might require DSI audit, if any. This is to be determined at this time.

8. Pediatric Development

The sponsor requests a waiver for the pediatric population as this disease does not afflict the pediatric population.

9. Summary

Novartis has submitted a 505(b)(1) application for glycopyrronium (GP) 12.5 mcg inhalation via the neohaler BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

The key studies in the clinical development program include; 2 phase 3 trials comparing GP 12.5 mcg inhalation BID vs. placebo evaluating FEV1 AUC (0-12h) at week 12 as the primary endpoint, 1 long term safety study (52 weeks) comparing GP 12.5 mcg BID to Indacaterol (Ind) 75mcg QD and 1 dose ranging study evaluating 12.5, 25, 50 and 100 mcg QD/BID doses of GP. Numerous supportive studies have also been submitted and are outlined in the body of this review.

The submission is fileable. There are no filing comments for the Sponsor.

10. Review Timeline

Milestones	Target date for completion
Filing date (60 days)	2/27/2015
74-day letters due if filed	3/13/2015
Mid-cycle review meeting	about 5/29/15
Primary review due/ Wrap-up mtg	9/24/2015
PDUFA goal	10/29/2015

11. Filing Checklist

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			

	Content Parameter	Yes	No	NA	Comment
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: A2208 Study Title: Sample Size: 388 Arms: GP 12.5 mcg QD/BID GP 25mcg QD/BID GP 50mcg QD/BID GP 100mcg QD/BID Location in submission: Section 5 Study Number: A2206 Study Title: Sample Size: 281 Arms: GP 100mcg QD GP 200mcg QD Pbo Location in submission: Section 5 Study Number: A2205 Study Title: Sample Size: 83 Arms: GP 12.5mcg QD GP 25mcg QD GP 50mcg QD GP100mcg QD Placebo Tiotropium 18mcg QD Location in submission: Section 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 A2317 Indication:	X			

	Content Parameter	Yes	No	NA	Comment
	long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema Pivotal Study #2 A2318 Indication: long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Adult Disease COPD
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

12. Comments for the 74-day letter

None

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

/s/

ERIKA N TORJUSEN
03/02/2015

BANU A KARIMI SHAH
03/02/2015