CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208437Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader/Division Director Review -Addendum

Date	November 13, 2017
From	Banu A. Karimi-Shah, MD Lydia Gilbert-McLain, MD
Subject	CDTL/DD Review - Addendum
NDA/BLA # **Supplement#**	NDA 208437
Applicant	Sunovion Pharmaceuticals
Date of Re-Submission	June 15, 2017
PDUFA Goal Date	December 15, 2017
Proprietary Name / **Established (USAN) names**	Lonhala Magnair/glycopyrrolate inhalation solution
Dosage forms / Strength	25 mcg inhalation solution
Proposed Indication(s)	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	*Approval*

1. Executive Summary

In the first review cycle, Sunovion submitted a 505(b)(2) New Drug Application (NDA) 208437 on July 29, 2016, for glycopyrrolate inhalation solution (GP, SUN-101, Lonhala Inhalation Solution) indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Lonhala is formulated as a solution for inhalation contained within a unit-dose vial, which is to be inserted into the PARI eFlow CS nebulizer (Magnair). The unit-dose, single use vial contains 25 mcg of glycopyrrolate (GP) in 1 mL. The proposed dose is one vial (25 mcg) by inhalation twice daily. The application was not approved in the first cycle as outlined below. The Applicant re-submitted the application on June 15, 2017.

Although the efficacy and safety data supported the approval of Lonhala Magnair for the maintenance treatment of airflow obstruction in patients with COPD, there were deficiencies in the biocompatibility evaluation of the Magnair device identified by CDRH in the original review cycle. These deficiencies related to the biocompatibility testing for the PARI eFlow closed system nebulizer. The biocompatibility testing provided in the NDA was inadequate and Sunovion was asked to provide new extractable and leachable testing during the review cycle. However one of the solvents used (the non-polar solvent) caused significant degradation of the test devices under both of the extraction conditions which rendered the data invalid. To address this deficiency, a revised toxicological risk assessment for all chemical compounds identified from the revised extractable and leachables testing was required. As a result, a Complete Response Action was taken on May 26, 2017.

To support the GP 25 mcg twice daily (BID) dose for COPD, Sunovion conducted a clinical program that included two dose-ranging trials, two confirmatory phase 3 clinical trials, and one supportive long-term safety trial. The CDTL and Division Director memoranda dated May 22, 2016, and May 26, 2016, provide an overview of the different aspects of this application. This memo serves as an addendum to those reviews, specifically focusing on the resolution of the deficiencies, which now support **Approval** of this application. This addendum provides an overview of the deficiencies outlined in the Complete Response Letter and a summary of the data submitted to resolve these deficiencies (as provided by the CDRH review).

2. Deficiencies Leading to a Complete Response Action

The following deficiencies were communicated to the Applicant in the CR letter dated May 26, 2017:

1. In your response to the Information Request dated, March 17, 2017, you provided two new chemical extractable and leachable (E&L) tests for the eFlow Closed System Nebulizer. Both tests were conducted using water as the polar extraction solvent and isopropanol (IPA) as the non-polar solvent. The extraction conditions used were identified as 50°C for 72 hours or 60°C under sonication for up to 24 hours. In the test reports provided, you stated that IPA used as the non-polar extraction solvent caused significant degradation of the test devices, under both of the two extraction conditions.

   The eFlow Closed System Nebulizer proposed is indicated for permanent use. In clinical use, the device will come into direct contact with the SUN-101 (glycopyrrolate) Inhalation Solution and patient's exhaled gases. When being exposed to such clinical conditions, both polar and non-polar chemical residues may potentially leach out from the device, which may pose significant health risks to patients when inhaled.

   As the IPA extraction solvent was demonstrated to be incompatible with the test device materials and caused device degradation, the test data from the IPA extracts are considered invalid. Thus your E&L testing provided is considered inadequate for the biocompatibility endpoints assessments for systemic toxicity and genotoxicity and inadequate to address the drug-device material compatibility.

   To address the safety concerns for the eFlow Closed System Nebulizer, provide a revised chemical E&L testing at 50°C for 72 hours, using an appropriate non-polar extraction solvent that is compatible with the test device and does not cause the device degradation. We recommend that you use a non-polar extraction solvent or a mixed solvent system that is chemically similar in polarity to the intended medications. Alternatively, you may provide the revised chemical testing based on the intended drugs or a surrogate chemical that has chemical properties similar to the drugs proposed. If a surrogate or non-polar solvent was used, provide your scientific rationale and justification for your choice of the surrogate or the non-polar solvent to demonstrate that the worst

clinical use condition is represented. In addition, clarify whether the surrogate or solvent used compromises the integrity of the tested device or representative component samples.

Provide a revised toxicological risk assessment (exposure and safety assessment) for all chemical compounds identified from the revised E&L testing, including organics, inorganics, organometallics, metals, and other residues. To address a worst case safety concern, the maximum amounts of the chemicals identified per device system should be considered in the risk assessment calculation. The risk assessment calculation should also take into consideration the inhalation exposure route, intended patient population, and a worst case scenario. For analysis of the chemical residues and the allowable limits, refer to the published toxicological literature for the reference doses, such as the no observed adverse-effect-levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), and/or to the inhalation protective values from the US based health organizations or WHO. For the risk assessment calculation, you may also refer to the FDA-recognized standard ISO 10993-17:2002(R)2012 Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances, and the TTC approaches described in the CDER ICH M7 guidance. Clearly identify the calculated margin of safety (MOS) value for each of the chemicals identified and describe in detail (step-by-step) how the MOS values were calculated. Provide a clear rationale for the uncertainty values that are used in the exposure and safety assessment for each chemical residue.

Be advised, if a safety signal (e.g. chemicals with MOS <1) is identified through your risk assessment of the chemical extractables and leachables, additional justification or biological testing may be warranted in order to address this risk.

2. Information to Resolve Deficiencies

In the re-submission, the Applicant provided the results of repeat extractables and leachables testing using appropriate solvents. The information was reviewed and deemed acceptable by the CDRH review team. Per their review, there are no further outstanding biocompatibility issues.

3. Other Outstanding Issues: Human Factors and Labeling

Human Factors

The CDRH review of the human factors data revealed a use error that occurred when the drug vials were pierced prior to inserting the aerosol head. There was concern that this could lead to medication leaking from the handset and subsequently, to patients receiving an incomplete dose of their prescribed medication. The CDRH review expressed concern that if this were to occur, the patient may be unaware that they did not receive the full dose, and may continue to use the

device incorrectly. This issue was communicated to the sponsor on October 6, 2017, and appropriate labeling changes were made in the Instructions for Use, to address this deficiency.

Labeling

The package insert, patient package insert, instructions for use, carton/container, and other instructional labeling has been reviewed by the appropriate labeling consultants. The label has been agreed upon with the Applicant.

4. Regulatory Action

The biocompatibility deficiencies which precluded approval in the first review cycle have been resolved. The efficacy and safety data support Approval of Lonhala Magnair for the maintenance treatment of airflow obstruction in patients with COPD.

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/s/

BANU A KARIMI SHAH
12/04/2017

LYDIA I GILBERT MCCLAIN
12/05/2017

SUMMARY REVIEW OF REGULATORY ACTION

Date:	May 26, 2017
From:	Lydia Gilbert-McClain, MD Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	208437
Applicant Name:	Sunovion Pharmaceuticals
Date of Submission:	July 29, 2016
PDUFA Goal Date:	May 26, 2017
Proprietary Name:	Lonhala Magnair
Established Name:	Glycopyrrolate delivered via the PARI eflow CS nebulizer
Dosage form:	Inhalation solution
Strength:	25 mcg glycopyrrolate per unit-dose vial
Proposed Indications:	Long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Action:	Complete Response

1. Introduction

Sunovion submitted a 505(b)(2) New Drug Application (NDA) 208437 on July 29, 2017, for glycopyrrolate inhalation solution (GP, SUN-101, Lonhala Inhalation Solution) indicated for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Lonhala is formulated as a solution for inhalation contained within a unit-dose vial, which is to be inserted into the PARI eFlow CS nebulizer (Magnair). The unit-dose, single use vial will contain 25 mcg of glycopyrrolate (GP) in 1 mL. The proposed dose is one vial (25 mcg) by inhalation twice daily.

To support the GP 25 mcg twice daily (BID) dose for COPD, Sunovion has conducted a clinical program that includes two dose-ranging trials, two confirmatory phase 3 clinical trials, and one supportive long-term safety trial. This memo provides an overview of the application, with a focus on the clinical data which demonstrate the efficacy and safety of GP 25 mcg BID in patients with COPD. Focus is placed on the trough FEV_1 (lung function), which was the primary endpoint in the lung function studies designed to demonstrate efficacy. This memo also addresses the recommendations from each of the individual review disciplines and consultants. Specifically, this memo summarizes the device biocompatibility deficiencies identified by CDRH which are the reason from the Complete Response action.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists, short- and

long-acting anticholinergics, combination products containing short- and long-acting beta-2 adrenergic agonists and short- and long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists and corticosteroids, products containing methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), and PDE-4 inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

GP is an anticholinergic drug which has been in clinical use for many years as tablets (Robinul 6 mg), or intra-operatively as an injectable (Robinul 100 mcg/injection every 2-3 minutes). In the United States, an oral formulation (Cuvposa) is indicated for severe drooling in patients 3-16 years of age with neurologic conditions (initial dose 0.02 mg/kg three times daily, titrated to a maximum 0.1 mg/ three times daily). There are three approved GP-containing products for COPD. GP was approved as a dry powder for inhalation both as a single ingredient (Seebri Neohaler, NDA 207923) and in combination with indacaterol (Utibron Neohaler, NDA 207930), as well as in fixed-combination with formoterol fumarate as a inhalation aerosol (Bevespi Aerosphere, NDA 208924)

Prior to the approvals of the other glycopyrrolate-containing products, inhaled anticholinergics were widely available in the U.S., including one short-acting anticholinergic, ipratropium bromide, and three long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler, Spiriva Respimat), aclidinium bromide (Tudorza Pressair), and umeclidinium (in combination with vilanterol as Anoro Ellipta, and as single ingredient Incruse Ellipta) . All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention.

In the past, safety concerns of stroke and cardiovascular death have been raised with the use of these drug products in patients with COPD, and thus have been the subject of previous FDA advisory committee meetings. [1] These concerns have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat. [2, 3] Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in a COPD program to limit high systemic exposure and potential safety concerns.

Regulatory interaction between the Agency and Sunovion:
Sunovion met with the Agency for the usual milestone meetings. Specifically, key regulatory interactions included:

[1] FDA Early Communication about Ongoing Safety Review of Tiotropium. http: //ww fda.gov/cder/drug/early_comm/tiotropium.htm
[2] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.
[3] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.

- Pre-IND Meeting: March 16, 2011
- Type C Meeting: June 20, 2012
- End-of-Phase 2 Meeting: October 17, 2013
- Type C Meeting: October 8, 2014
- Pre-NDA Meeting: May 11, 2016

The main topic for discussion at earlier meeting was dose selection. Specifically, at the End-of-Phase 2 Meeting, the Division recommended that further dose exploration was necessary. The Division also recommended the evaluation of MACE and stroke-related events as part of the safety analysis in phase 3.

3. Chemistry, Manufacturing, and Controls

This application consists of a drug product that is part of a drug/device combination. The drug product (GP, Lonhala) is proposed to be co-packaged with the device (PARI eFlow CS nebulizer, Magnair).

Drug Product and Drug Substance

Glycopyrrolate USP, the active component of Lonhala Inhalation Solution, is a synthetic quaternary ammonium compound that acts as a competitive antagonist at muscarinic acetylcholine receptors. Glycopyrrolate, C19H28BrNO3, is a white, odorless, crystalline powder that is soluble in water and in alcohol.

The drug product, Lonhala Inhalation Solution, is supplied in low-density polyethylene (LDPE) unit-dose vials, each containing 1.0 mL of the solution. Each vial contains 25 mcg of glycopyrrolate in sterile, isotonic saline, pH-adjusted to 4.0 with citric acid and sodium hydroxide. The active ingredient, glycopyrrolate (GP), is very soluble in the buffer. All the excipients are commonly used for inhalation/injection products and at levels within that of already approved products. The drug product is sterilized (b) (4) . Extractables and leachables have been studied and have been found to be adequately low. The drug product manufacturer, Holopack, is a contract manufacturer and the associated facility was found to be acceptable. Stability studies support the expiry of 24 months.

The information for the drug substance is mainly provided by reference to two drug master files (DMF (b) (4)), both of which has been reviewed and have been found to be acceptable. The drug substance is manufactured at two facilities by two separate firms and both were deemed acceptable based on their inspectional history and manufacturing capability.

Device

The drug product is intended to be delivered using a specific nebulizer device co-packaged and co-marketed with the inhalation solution drug product. The device is an eFlow® Closed System nebulizer, referred to as eFlow CS. The eFlow CS is a portable, hand-held, electronic nebulizer intended for single patient use that uses a vibrating perforated membrane to generate an inhalation aerosol. The eFlow CS device including

the nebulizer handset (hand-held unit, with installed aerosol head and drug vial), the connection cord, the controller, and the AC adapter, and 2 additional drug vials are shown below.

Figure 1. The eFlow Closed System Nebulizer

The eFlow CS is intended for single patient use to deliver GP Inhalation Solution drug product by patients who self-administer treatments at home, by caregivers, and in nursing homes and hospitals by healthcare professionals. The eFlow CS is a modified version of three PARI Respiratory Equipment (PRE) FDA-cleared electronic nebulizers: the TRIO®, the Altera®, and the eRapid®.

The eFlow CS technology uses a wafer-thin plate of stainless steel (the membrane), which is perforated with numerous laser-drilled holes. This micro-perforated membrane vibrates at high frequencies against a reservoir of liquid (i.e., drug product). The vibration source is the piezoelectric actuator that is activated by an electronic drive circuit. The actuator and the perforated membrane are the main components of the aerosol head that is in contact with the liquid medication to be aerosolized. Liquid jets are created as an inertial response to the vibration of the membrane. Surface tension and hydrodynamic effects then cause these jets to disperse to produce a stream of precisely controlled droplets.

The eFlow Closed System Nebulizer (eFlow CS) is manufactured by PARI Respiratory Equipment (PRE). Sunovion offers two commercial configurations that include a starter kit and a refill kit. The Office of Compliance at CDRH also finds the application to be approvable from a Quality Systems Requirements perspective.

The manufacturer of the eFlow CS has similar versions of the device which have been previously 510(k) cleared, as an open system nebulizer not intended to be used with a specific drug formulation. While the eFlow CS proposed under the current NDA submission has similar operating principles and components, it has undergone modifications to the controller, nebulizer handset, reservoir cap, and aerosol head. These changes can impact the performance, electrical safety, and biocompatibility of the device and required a new device review. To aid in the device review, additional sub-consults

were sent to the following review areas within CDRH: human factors, electrical safety, device biocompatibility, cleaning/disinfection, and software.

- The human factors validation study identified one situation which may lead to potential high severity harm. This use error occurred when the drug vials were pierced prior to inserting the aerosol head and may cause medication to leak from the handset and patients to receive an incomplete dose of their prescribed medication. If this occurs, the patient may be unaware that they did not receive the full dose, and may continue to use the device incorrectly. The clinical team in CDER felt that this deficiency was addressed by the scope of the clinical program. I agree with the clinical team's assessment. Furthermore, the product is intended for chronic maintenance use and not for acute treatment of symptoms. The device errors described can be handled with appropriate language in the patient instructions for use section of labeling.

- A biocompatibility issue was identified and communicated to the Applicant in December 2016. The Applicant provided their response in January 2017; upon review, CDRH identified outstanding issues for biocompatibility and cleaning. The Applicant provided information through interactive review which adequately addressed the outstanding concerns for cleaning by removing their optional disinfection procedure. They also submitted new extractables and leachables (E&L) testing to address the outstanding biocompatibility concerns. However, the new E&L testing resulted in significant degradation of the test article for their non-polar solvent used. This degradation invalidates these test results. E&L testing with toxicological risk assessment was conducted in lieu of genotoxicity, implantation, and systemic toxicity tests per ISO 10993. Therefore, CDRH has determined that in order to support the device biocompatibility based on the results of their E&L testing, the Applicant will need to repeat the testing using an appropriate non-polar solvent which does not degrade the device material. It is this deficiency that is the basis of the Complete Response action.

4. Nonclinical Pharmacology and Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues at this time.

The Applicant is pursuing a 505(b)(2) NDA pathway, relying on nonclinical safety information from previous glycopyrrolate NDAs to support their application and labeling. The nonclinical information relies on previously demonstrated safety from approved products Robinul Injection (NDA 17-558), Robinul Tablets (NDA 12-827), and Cuvposa oral solution (NDA 22-571). The Applicant conducted additional inhalation toxicology studies to support the new inhalation route of administration. However, during development of SUN-101 Inhalation Solution, other inhalation glycopyrrolate products were approved, lessening the essential need for the Applicant's nonclinical inhalation studies. These products were formulated as a dry powder (Seebri Neohaler; NDA 207923), dry powder in combination with indacaterol (Utibron Neohaler; NDA 207930),

and an aerosol in combination with formoterol fumarate (Bevespi Aerohaler NDA 208294). Furthermore, during the NDA review cycle, the Applicant notified the FDA on March 16, 2017 (SD-15) that they acquired ownership of Seebri Neohaler on January 27, 2017. Utibron Neohaler was also acquired, effective January 27, 2017. The Applicant now owns data that supported the approval of these two 505(b)(1) applications.

Due to the reliance on previously approved glycopyrrolate products for safety through the 505(b)(2) pathway, few nonclinical studies were submitted. The nonclinical program consisted of 1-month repeated-dosing inhalation studies in rats and dogs, followed by a 6-month repeated-dosing inhalation study in rats. The applicant acquired ownership of Seebri Neohaler on January 27, 2017 (during the application review period), and could rely solely on that data to support the safety of glycopyrrolate for the inhalation route of administration. The Applicant's nonclinical
inhalation toxicity studies, conducted prior to approval of any inhalation product for glycopyrrolate, produced results that were generally similar to those approved products.

The toxicities in the rat associated with inhaled glycopyrrolate in 1- and 6-month studies included reduced body weight and food intake; dilated pupils; increased red blood cell counts, hemoglobin, and hematocrit; increased lung weight associated with alveolar macrophages; laryngeal inflammation; and increased porphyrin secretion of the Harderian gland. The following findings were observed in the 1- month inhalation study in dogs: dilated pupils, dry mouth, reduced body weight and food consumption, emesis, and thymus atrophy with a reduction in thymus weights. All these effects were partly or completely reversible during a recovery phase.

Two impurities of the drug substance, α-cyclopentylmandalic acid (CPMA) and benzoic acid, were also assessed for safety. Neither of these compounds were detected in the drug substance used in the 6-month inhalation study and these were not tested for their presence in the earlier drug substance used in the 1-month inhalation studies in rats and dogs. CPMA is also a major human metabolite of glycopyrrolate formed upon hydrolysis of glycopyrrolate. CPMA lacks the pharmacological profile of GP, but its potential pharmacology and toxicity is unknown. The safety of CPMA is confounded with the safety of glycopyrrolate due to CPMA's unavoidable presence as a metabolite in humans. Benzoic acid is a potential oxidative degradant that was formed in forced degradation studies. These two compounds lack mutagenic structural alerts and are negative in genotoxic tests. While the systemic safety of CPMA is established, the local safety from inhalation of CPMA has not been established and the specifications were
reduced from those proposed by the Applicant to those requested by the CMC reviewer to NMT(b) (4) % for both compounds.

Pregnancy risk summary in the product labeling for GP-containing drugs states that "there are no adequate and well-controlled studies in pregnant women." This was formerly known as Pregnancy Category C.

5. Clinical Pharmacology and Biopharmaceutics

The Applicant supports this NDA submission with 3 three key clinical pharmacology studies, including two dose-ranging studies (EP-101-104 and SUN101-201) and one PK study (SUN101-105) with the CS eFlow® nebulizer. These studies used the same nebulizer system as proposed in the to-be-marketed product. The Applicant conducted three additional exploratory dose-ranging studies (EP-101-01, EP-101-02 and EP-101-103) with an open-system (OS) eFlow® nebulizer prior to proceeding with the two pivotal dose-ranging studies (i.e., EP-101-104 and SUN101-201). The dose-ranging studies will be discussed in more detail in the clinical efficacy section.

The following are the major findings from the current review:

1) Following administration of glycopyrrolate inhalation solution via CS eFlow® nebulizer, the median Tmax for glycopyrrolate occurs around approximately 20 minutes and the elimination half-life is approximately 5 hours.
2) The systemic exposure following single-dose administration of glycopyrrolate inhalation solution (50 mcg) in subjects with moderate to severe COPD was approximately 5- to 6-fold lower as compared to that attained following single-dose administration of Cuvposa® Oral solution in healthy adults under fasted conditions (cross-study comparison, Cuvposa® oral solution data is from its prescribing label).
3) Neither age, body weight, race, nor ethnicity had relevant effects on drug exposure.

6. Clinical Microbiology

The Applicant provided an adequate description of the drug product composition and the container closure system and how product sterility would be maintained. Container-closure integrity testing is performed on 100% of manufactured vials during commercial production and any leaking vials are rejected. This is consistent with regulatory expectations for a sterile pharmaceutical product. The microbial attributes of the drug product and drug product manufacturing were assessed and found to be acceptable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant clinical studies with glycopyrrolate inhalation solution in COPD patients

Study ID *Dates*	Design/ Duration	Treatment Arms†	N (ITT)	Efficacy Variables	Sites *% US Sites*
Dose-ranging studies – COPD patients					
EP-101-04 *Oct 2012-* *April 2013*	- R, DB, PG, PC - mod/svr COPD - FEV_1 30-70% - 42 to 75 yrs. old - 28 days	GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Placebo BID *Serial Spirometry Substudy* GP 12.5 mcg BID GP 25 mcg BID GP 50 mcg BID GP 100 mcg BID Placebo BID	55 54 57 59 57 26 24 25 26 24	FEV_1 Trough	US (*100%*)
SUN101-201 *Jan 2014-* *May 2014*	-R, DB, PC -XO, OL, AC - mod/svr COPD - FEV_1 40-70% - 40 to 65 yrs. Old - 7 days	GP 3 mcg BID GP 6.25 mcg BID GP 12.5 mcg BID GP 50 mcg BID Aclidinium 400 mcg BID‡ Placebo BID	91 92 89 92 92 92	FEV_1 Trough	US (*100%*)
Pivotal bronchodilator (lung function) efficacy and safety studies – COPD patients					
SUN101-301 *Feb 2015-* *Nov 2015*	- R, DB, PG, PC - mod/svr COPD - 42 to 87 yrs. old - FEV_1 20-79% - 12 weeks	GP 25 mcg BID GP 50 mcg BID Pbo BID *Serial Spirometry Substudy* GP 25 mcg BID GP 50 mcg BID Placebo BID	217 218 218 49 62 42	FEV_1 Trough	US (*100%*)
SUN101-302 *Feb 2015-* *Dec 2015*	- R, DB, PG, PC - mod/svr COPD - 40 to 84 yrs. old - FEV_1 20-79% - 12 weeks	GP 25 mcg BID GP 50 mcg BID Pbo BID	214 214 212	FEV_1 Trough	US (*100%*)
Supportive long-term safety studies – COPD patients					
SUN101-303 *Oct 2014-* *Feb 2016*	-R, OL, PG, AC - mod/svr COPD - 41-89 yrs. old - FEV_1 15-80% - 48 weeks	GP 50 mcg BID Tiotropium 18 mcg QD♦	620 466	Adverse Events/Safety	Czech Republic, Hungary, Russia, US *(90%)*

† All GP treatments administered via the eFlow CS nebulizer; ‡Aclidinium administered via Tudorza Pressair; ♦Tiotropium administered via Spiriva HandiHaler; R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, OL=open label, AC=active control, CO=cross over, WO=wash out, BID=twice daily, GP = glycopyrrolate (Lonhala inhalation solution), Pbo= placebo; FEV1 trough was the average of the 23.5 and 24 hour measurements collected after the in-clinic morning dose of study medication

Dose Ranging Studies: EP-101-04 (Study 04) and SUN101-201 (Study 201)

The dose ranging studies were designed to characterize the dose-response for glycopyrrolate (GP). The study designs, treatment arms, and primary efficacy variable measured are shown in Table 1.

Study 04 assessed the efficacy of GP 12.5, 25, 50, and 100 mcg administered BID via the eFlow CS nebulizer, in a placebo-controlled, 28-day, parallel group study in patients with moderate-to-severe COPD. The primary efficacy endpoint was the change from baseline in morning trough FEV_1. The results of Study 04 are shown in Figure 1 and Table 2 below.

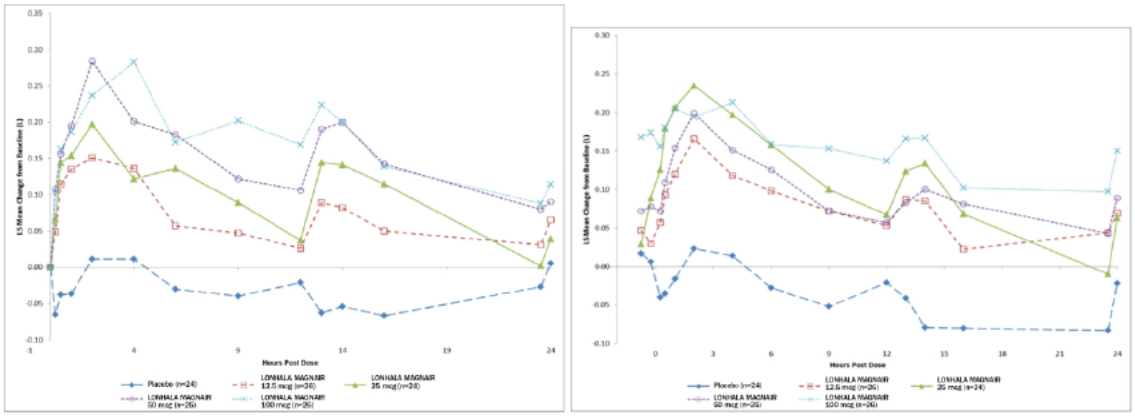

Figure 1. Mean change from baseline in trough FEV_1 on Day 1 (left) & Day 28 (right) -Study 04

Table 1. Mean change from baseline in trough FEV_1(L) – Dose-ranging Study 04 (ITT)

Treatment	N	LS Mean (SE)	Treatment Difference vs. Placebo	
			LS Mean (95% CI)	p-value
GP 12.5 mcg BID	55	0.106 (0.03)	0.117 (0.037, 0.197)	<0.01
GP 25 mcg QD	54	0.117 (0.03)	0.128 (0.048, 0.209)	< 0.01
GP 50 mcg BID	57	0.135 (0.03)	0.146 (0.067, 0.226)	< 0.01
GP 100 mcg BID	59	0.166 (0.03)	0.177 (0.099, 0.255)	< 0.01
Placebo	57	-0.011 (0.03)	--	--

Statistics are from a mixed model for repeated measures with fixed factors for treatment, visit, inhaled corticosteroid use, substudy participation, an interaction for visit by treatment; a covariate for baseline FEV1; and a random factor for subject.
Morning trough is the average of the 23.5 and 24 hour values.
N = ITT population
The results of this study are reported as Study A in Section 14 of the package insert.

The results of Study 04 demonstrated efficacy for all tested doses of GP, including the lowest dose of 12.5 mcg BID. Therefore, Study 201, a 7-day crossover study, was conducted to better characterize and explore the lower end of the dose-response. Study 201 explored the efficacy of GP 3 mcg, 6.25 mcg, 12.5 mcg, and 50 mcg, administered BID via the eFlow CS nebulizer. The study was double-blind for GP and placebo, and included an open-label aclidinium bromide treatment arm as an active control. Upon review of the results of Study 201, the Division concluded that the lower end of the dose-response relationship had been adequately explored; based on the results of the dose-ranging studies, the Division agreed with carrying both the 25 mcg and 50 mcg BID doses of glycopyrrolate into the phase 3 program.

Confirmatory Studies: Studies SUN101-301 (Study 301) and SUN101-302 (Study 302)

Studies 301 and 302 were 12-week, randomized, double-blind, placebo-controlled studies designed to evaluate the safety and efficacy of GP 25 mcg and GP 50 mcg administered twice daily via the eFlow CS nebulizer in patients with moderate to severe COPD.

Studies 301 and 302 enrolled adult male and female subjects ≥ 40 years of age with a clinical diagnosis of moderate-to-very severe COPD according to the GOLD 2014 guidelines. Subjects were current or ex-smokers with ≥ 10 pack-year smoking history, with a post-bronchodilator FEV1 of < 80% of predicted normal and greater than 0.7 L, an FEV1/FVC ratio less than 0.70, and had the ability to perform reproducible spirometry according to the ATS/ERS guidelines.

The primary endpoint in both studies was the change from baseline in trough FEV_1 at Week 12. The baseline FEV_1 was defined as the mean of the pre-dose FEV_1 measured 45 and 15 minutes prior to dosing on Day 1. Trough FEV1 was defined as the mean of the two FEV1 values obtained at 23 hours 30 minutes and 24 hours after the in-clinic morning dose (i.e., approximately 12 hours after the previous evening dose).

Baseline demographics were fairly balanced across treatment groups and were generally representative of the population in whom COPD is known to occur. The median age for the two studies ranged from 63-64 years, with the majority being white (86-92%) males (51-59%), <65 years of age (50-62%). These studies were conducted fully in the United States. Of the study population, 7% to 13% were black patients.

Most patients completed the study (88-94%) on treatment (81-89%). The number of patients who discontinued from treatment and the study was also fairly balanced, with higher premature discontinuations in the placebo group. The most common reason for premature discontinuation from the study was withdrawal by subject.

Studies 301 and 302 were the primary studies that support the bronchodilator claim for Lonhala Magnair. Results from the primary efficacy analysis from these studies showed statistically significant differences between Lonhala Magnair and placebo for both GP 25 mcg and 50 mcg doses. FEV_1 time profile curves for Studies 301 and 302 also showed

consistent efficacy over time. The curves for Study 301 are shown below in Figure 3; the curves for Study 302 showed similar results. There was no meaningful difference between the 25 mcg and 50 mcg doses, and therefore, the Applicant proposed the lower dose for registration.

Table 3. Primary Efficacy Results: LS Mean Difference in Change From Baseline in Trough FEV_1 (L) at Week 12 (ITT) – Studies 301 and 302

		Treatment Difference		
Study Treatment	**CFB in Trough FEV_1 LS Mean (SE)**	**LS Mean (SE) Vs. Placebo**	**95% CI**	**p-value**
Study 301				
GP 25 mcg BID N=217	0.089 (0.014)	0.096 (0.019)	(0.059, 0.133)	<0.0001
GP 50 mcg BID N=218	0.096 (0.014)	0.103 (0.019)	(0.066, 0.141)	<0.0001
Placebo N=218	-0.008 (0.014)	-	-	-
Study 302				
GP 25 mcg BID N=214	0.092 (0.014)	0.081 (0.020)	(0.042, 0.120)	<0.0001
GP 50 mcg BID N=214	0.085 (0.014)	0.074 (0.020)	(0.035, 0.113)	0.0002
Placebo N=212	0.011 (0.015)	-	-	-

BID = twice daily; CFB = change from baseline; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intent to treat; L = liter(s); LS = least squares;; SE = standard error, N= ITT population ; CFB = Change from Baseline. Source: Module 5.3.5.1, SUN101-301 CSR, Table 19, Page 100, Table 14.2.1.2, Page 216, SUN101-302 CSR, Table 14.2.1.2, Page 173

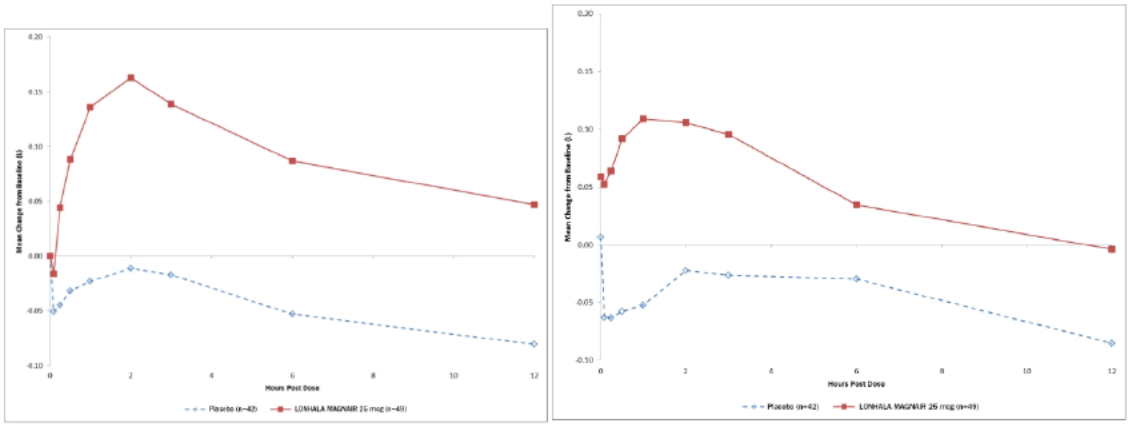

Figure 3. Mean change from baseline in FEV_1(L) over time on Day 1 (left) & Day 84 (right) - Study 301

Subgroup analyses on the primary endpoints were conducted by gender, age, race, airflow limitation, smoking status, and ICS use. In general, the subgroup analyses were consistent with the primary results from the overall population.

The St. George's Respiratory Questionnaire (SGRQ) is a patient-reported outcome instrument which measures symptoms, activities, and the impact of disease on daily life

in patients with COPD. The minimal clinical important difference (MCID) for the SGRQ has been determined to be 4 points for COPD patients. The SGRQ was assessed as a secondary endpoint in both studies 301 and 302. In Study 301, the SGRQ responder rate for the LONHALA MAGNAIR 25 mcg treatment arm was 50% compared to 40% for placebo [Odds Ratio: 1.49; 95% CI: 0.97, 2.27]. In Study 302, the SGRQ responder rate for the LONHALA MAGNAIR 25 mcg treatment arm was 44% compared to 30% for placebo [Odds Ratio: 1.91; 95% CI: 1.22, 2.98]. The responder rates and odds ratios for the 50 mcg treatment are shown in Table 4 as well.

Table 4. SGRQ Responder Analysis at Week 12- Studies 301 and 302

Study 301			
	Placebo BID N = 218	**GP 25 mcg BID N = 217**	**GP 50 mcg BID N= 217**
# of subjects with evaluable data	179	189	179
Responders, n (%)	71 (39.7)	94 (49.7)	79 (44.1)
Non-responders, n(%)	108 (60.3)	95 (50.3)	100 (55.9)
Odds Ratio (95% CI)		1.49 (0.94, 2.27)	1.22 (0.79, 1.87)
Study 302			
	Placebo BID N = 212	**GP 25 mcg BID N = 217**	**GP 50 mcg BID N = 217**
# of subjects with evaluable data	186	183	188
Responders, n(%)	55 (29.6)	80 (43.7)	74 (39.4)
Non-responders, n(%)	131 (70.4)	103 (56.3)	114 (60.6)
Odds Ratio (95% CI)		1.91 (1.22, 2.98)	1.54 (0.99, 2.40)

Source: Statistical Review Mingyu Xi, PhD.

Efficacy Conclusions

The Applicant provides support for the efficacy of GP 25 mcg BID for the maintenance treatment of COPD by demonstrating a statistically significant improvement in lung function in terms of change from baseline in trough FEV_1 compared to placebo in two replicate 12-week studies. The efficacy of GP 25 mcg BID was also supported by other measures of lung function and health-related quality of life, as measured by the SGRQ.

The clinical and statistical review teams are in agreement that the data provided are adequate to support the efficacy of GP 25 mcg BID (Lonhala Magnair; SUN101) for the maintenance treatment of airflow obstruction in patients with COPD.

8. Safety

a. Safety database

The safety assessment of Lonhala Magnair is based on the studies shown in Table 1. The safety database for Lonhala Magnair was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Lonhala Magnair for use as maintenance treatment of airflow obstruction in patients with COPD.

The safety evaluation of GP relies primarily on 3-month data from Studies 301 and 302. Pooling of data across the two 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 doses of GP received (25 and 50 mcg BID). Safety assessments included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. In addition, a long-term safety study (Study 303) was conducted, and did not reveal any additional safety signals.

The 3-month safety database included 1,293 COPD patients; 431 treated with GP 25 mcg BID, 432 patients treated with GP 50 mcg BID, and 430 patients treated with placebo.

Few patients discontinued treatment prematurely in the GP development program. Study drug withdrawal occurred more frequently in the placebo group compared to GP 25 mcg and 50 mcg groups, respectively [n=40 (9.3%), n=22 (5.1%), n=17 (3.9%)]. The most common AE leading to discontinuation were events occurring in the respiratory, mediastinal and thoracic system organ class (SOC). Overall, adverse events were not a significant cause for patient discontinuation. Death was a rare occurrence, with one event (diastolic dysfunction, COPD exacerbation, pulmonary hypertension) occurring in the high dose (50 mcg) dose group in the 3-month studies. The overall occurrence of SAEs was low and fairly balanced across GP 25 mcg and GP 50 mcg treatment groups, respectively [n=13 (3.0%), n=18 (4.2%)] with more events occurring in the placebo group [n=24 (5.6%)]. In general, the numbers of patients experiencing individual SAEs were small, and without meaningful imbalances.

Adverse events of special interest (AESI) were identified by the Applicant based upon known class effects for anti-muscarinic drugs which included pneumonia, anticholinergic syndrome, cardiovascular, cerebrovascular, gastrointestinal obstruction, glaucoma-related, and adjudicated major adverse cardiovascular events (MACE). As expected, anticholinergic events (e.g. dry mouth, dizziness, blurred vison) were reported more frequently in the GP treatment arms compared to the placebo arms and appeared to be dose-related. The most frequently reported anticholinergic AE was dry mouth [n=1 (0.2%) subject in the placebo group, n=4 [0.9%] subjects in the GP 25 mcg BID group, and 7 [1.6%] subjects in the GP 50 mcg BID group). Cardiovascular events of special interest occurred more frequently in the placebo group compared to the GP 25 mcg and 50 mcg treatment arms, respectively [n=11 (2.6%), n=7 (1.6%), n=9 (2.1%)]. MACE was reported in 5 subjects, which included 3 subjects (0.7%) who received GP 50 mcg, 2 subjects (0.5%) who received placebo, and 0 subjects who received GP 25 mcg. Cerebrovascular events were rare and fairly balanced across the treatment groups [GP 25mcg n=3 (0.7%), GP 50 mcg n=1 (0.2%), placebo n=2 (0.5%)]. Gastrointestinal obstruction AEs were reported for only 1 (0.2%) subject in the GP 25 mcg group (small intestinal obstruction), while no subjects in the placebo or GP 50 mcg BID groups reported an AE related to gastrointestinal obstruction. Glaucoma-related AEs were reported in 3 subjects with vision blurred in 2 (90.5%) subjects who received GP 25 mcg and eye pain in 1 (0.2%) subject who received 50 mcg. Overall, these differences were small and not clinically meaningful.

Adverse events were generally balanced between the GP and placebo groups. Common adverse events occurring in ≥ 2% of patients and at a higher incidence than placebo included dyspnea 4.9% vs. 3.0%) and urinary tract infection (2.1% vs. 1.4%). Adverse events occurring in 1-2% of patients and more commonly in GP 25 mcg vs. placebo included wheezing, upper respiratory tract infection, nasopharyngitis, and fatigue. The findings from the long-term safety study were consistent with the results seen for the primary 3 month safety database.

c. REMS/RiskMAP

Sunovion submitted a Risk Management Plan for Lonhala Magnair, which consists of routine pharmacovigilance practices. A REMS is not necessary for Lonhala Magnair.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was neither convened nor required for this submission as the safety and efficacy of an anticholinergic such as GP in the maintenance treatment of COPD is well-described and well-understood.

10. Pediatric

Sunovion is requesting a claim for GP for COPD. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required. The PeRC had previously agreed that for such COPD applications, a full waiver should be granted because studies would be impossible or highly impracticable, since the disease entity of COPD does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All trials were conducted in accordance with accepted ethical standards. An evaluation of effect size by site did not reveal any sites which enrolled a disproportionally large number of patients and/or had a treatment effect that was much different than the overall treatment effect. This was a large clinical development program that enrolled relatively small numbers of patients at each clinical site. Therefore, it is unlikely that one clinical site would drive the treatment effect. In addition, glycopyrrolate is known clinical entity (as stated above). For all these reasons, an OSI inspection was not conducted for this application.

b. Financial Disclosure

Appropriate financial disclosure information was provided by the Applicant. None of the investigators reported any proprietary interests. Two investigators reported significant payments ; however, given the international scope of this clinical development program, and the relatively low percentage of overall recruitment from these two investigators, any potential conflict of interest is not likely to impact study results.

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c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

Sunovion submitted Lonhala Magnair as the proposed proprietary name, which was accepted by DMEPA. As this application will not be approved in this review cycle, Sunovion will need to submit another proprietary name request in the future.

b. Physician Labeling

Sunovion submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. Labeling will be finalized once the biocompatibility issues are resolved.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Lonhala Magnair will have appropriate patient labeling to guide patients on the instructions for use.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Although the efficacy and safety data support the approval of Lonhala Magnair for the maintenance treatment of airflow obstruction in patients with COPD, there were deficiencies in the biocompatibility evaluation of the Magnair device. These deficiencies relate to the biocompatibility testing for the PARI eFlow closed system nebulizer. The biocompatibility testing provided in the NDA was inadequate and Sunovion was asked to provide new extractable and leachable testing during the review cycle. However one of the solvents used (the non-polar solvent) caused significant degradation of the test devices under both of the extraction conditions which rendered the data invalid. Sunovion will need to address this deficiency by providing a revised toxicological risk assessment for all chemical compounds identified from the revised extractable and leachables testing. Because of this deficiency, the regulatory action for this application is a Complete Response.

b. Risk-Benefit Assessment

From a clinical standpoint, the overall risk benefit assessment supports the approval of Lonhala Magnair (GP inhalation solution) 25 mcg BID for the long-term, maintenance treatment of airflow obstruction in patients with COPD. However, the Applicant has not adequately evaluated the biocompatibility of the Magnair device.

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c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

None.

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/s/

LYDIA I GILBERT MCCLAIN
05/26/2017