EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/686121/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orkambi

International non-proprietary name: LUMACAFTOR / IVACAFTOR

Procedure No. EMEA/H/C/003954/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

BCS Biopharmaceutics Classification System

CHMP Committee for Medicinal Products for Human use

CQA Critical Quality Attribute

DoE Design of experiments

FT-IR Fourier transform infrared spectroscopy

GC-MS Gas chromatography mass spectrometry

HPLC High performance liquid chromatography

HPMCAS Hypromellose acetate succinate

HS-GC Headspace Gas Chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IR Infrared

KF Karl Fischer titration

LDPE Low density polyethylene

LIW Loss in weight

MAA Marketing Authorisation Application

NIR Near Infrared Spectroscopy

NMR Nuclear Magnetic Resonance

Ph. Eur. European Pharmacopoeia

PAT Process Analytical Technology

PCTFE Polychlorotrifluoroethylene

PVC Poly vinyl chloride

QbD Quality by design

QTPP Quality target product profile

RH Relative Humidity

SDD Spray Dried Dispersion

SmPC Summary of Product Characteristics

TSE Transmissible Spongiform Encephalopathy

TSWG Twin screw wet granulation

USP United States Pharmacopoeia

USP/NF United States Pharmacopoeia/National Formulary

UV Ultraviolet

XR(P)D X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vertex Pharmaceuticals (Europe) Limited submitted on 5 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Orkambi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

Orkambi, was designated as an orphan medicinal product EU/3/14/1333 on 22 August 2014. Orkambi was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis

The applicant applied for the following indication:

Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene (see sections 4.4 and 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Lumacaftor was considered to be a new active substance and that ivacaftor was considered to be a known active substance.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0337/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0337/2014 not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance lumacaftor contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 29 January 2013, 05 June 2013, 29 November 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Greg Markey Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 5 November 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 23 October 2014
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 February 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 February 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 12 March 2015.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 March 2015. The evaluation timetable was reverted to a standard timetable.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2015
- The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GMP inspection at one manufacturing site performing finished product manufacturing and quality control in the United States between 14th and 16th of April 2015 and at one manufacturing site performing finished product manufacturing and quality control of the active substance and finished product in the United States between 13th and 16th of July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 July 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 9 July 2015.
- During the CHMP meeting on 20-23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2015.
- During the meeting on 21-24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Orkambi.
- The CHMP adopted a report on similarity of Orkambi with Kalydeco and Bronchitol on 24 September 2015

- The New Active Substance Report was adopted at the CHMP on 24 September 2015

2. Scientific discussion

2.1. Introduction

Cystic fibrosis (CF) is a chronically debilitating, autosomal recessive disease associated with serious morbidity and a high rate of premature mortality and at present, there is no cure. CF affects approximately 70,000 individuals worldwide, including approximately 30,000 individuals in the United States (US), 32,000 individuals in the European Union (EU), 4,000 individuals in Canada, and 3,100 individuals in Australia. The incidence and prevalence of CF varies between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.

CF is caused by mutations in the CF transmembrane conductance regulatory (CFTR) gene that result in absence or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride ion (CL-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the regulation of salt and water absorption and secretion. CFTR mutations can be classified according to the mechanisms by which they disrupt CFTR function. Stop codon mutations (class I) result in a truncated nonfunctional CFTR, class II mutations consist of aberrantly folded CFTR protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the CFTR protein and, consequently, the absence of CFTR function. These three classes usually lead to a classic CF phenotype with pancreatic insufficiency. CFTR mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal CFTR. These latter two classes are mostly associated with a milder expression of the disease. The most prevalent mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR) and it is a Class II mutation: it prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. The decrease in the amount of F508del-CFTR at the cell surface is due to a defect in the processing and trafficking of the F508del-CFTR protein. The very small amount of F508del-CFTR protein that reaches the cell surface also has defective channel gating and a decreased stability at the cell surface. Patients who are homozygous with F508del-CFTR defects have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease. The failure of the mutated CFTR to function properly in the lungs result in a cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs and eventually respiratory failure, the most common cause of death for patients with CF. The predicted median age of survival of individuals born with CF today is approximately 40 years of age, while the median age at death is generally in the 20s.

Lumacaftor has been clinically developed in combination with ivacaftor as a fixed dose combination (FDC) tablet for oral administration for the treatment of CF. Lumacaftor is a new active substance, while ivacaftor is a known active substance that is authorised for the treatment of CF in patients aged 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

Lumacaftor (LUM; VX-809) is a CFTR corrector and ivacaftor (IVA; VX-770; Kalydeco) is a CFTR potentiator. LUM acts on CFTR to facilitate the cellular processing and trafficking of CFTR, allowing the protein to reach the cell surface, where it exhibits improved chloride channel function compared to

uncorrected F508del-CFTR. The channel gating activity of F508del-CFTR that has been delivered to the cell surface by LUM can be potentiated by IVA to further enhance chloride transport. The combination of a CFTR corrector and potentiator is a novel approach to enhance the amount and function of the defective CFTR protein in patients with CF who have the F508del-CFTR mutation.

The proposed indication is the treatment of “cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene”. The proposed posology is two tablets of the fixed dose combination of lumacaftor 200mg/ivacaftor 125mg to be taken orally every 12 hours (lumacaftor 800mg/ivacaftor 500mg total daily dose).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets for oral administration containing 200 mg of lumacaftor and 125 mg ivacaftor as active substances.

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate, povidone K30, sodium laurilsulfate, magnesium stearate.

Coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, carmine (E120), brilliant blue FCF aluminum lake (E133), indigo carmine aluminum lake (E132).

Printing ink: shellac, iron oxide black (E172), propylene glycol, ammonium hydroxide.

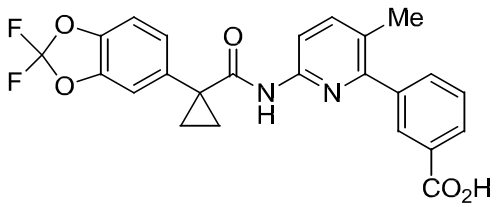
The product is available in blisters consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminium foil lidding as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Lumacaftor

General information

The chemical name of lumacaftor is 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid and has the following structure:



Molecular formula: $C_{24}H_{18}F_2N_2O_5$ - Molecular weight: 452.41 $gmol^{-1}$

Lumacaftor has a non-chiral molecular structure.

The structure has been confirmed by elemental analysis, ^{1}H-, ^{13}C- and two dimensional NMR spectroscopy, IR, Raman and UV spectroscopy, high resolution mass spectrometry and crystallographic analysis.

The active substance is a white to off-white non-hygroscopic crystalline solid. It is practically insoluble in water, buffer solutions with pH 1.0-8.0, simulated intestinal fluids and *n*-heptane, sparingly soluble in *n*-butanol and freely soluble in 2-methyltetrahydrofuran and formic acid.

Multiple polymorphic forms have been identified for lumacaftor. Form I has been used in all lumacaftor clinical trials and was selected for the manufacture of the drug substance used in the commercial drug product. This is the form consistently produced by the proposed manufacturing process and it has been demonstrated that it is stable upon storage in both active substance and finished product under the proposed storage conditions.

Since lumacaftor is considered a BCS class II, the drug substance was jet-milled early in development to reduce the particle size and potentially improve bioavailability. Based on these studies a control on lumacaftor particle size in the drug substance specification was established.

Manufacture, characterisation and process controls

A Quality by Design (QbD) strategy was pursued for the development of lumacaftor drug substance.

Lumacaftor is synthesized in nine main steps including seven chemical transformations in a convergent synthesis, followed by recrystallization and milling, using commercially available well defined starting materials with acceptable specifications. There are different suppliers for each starting material. However, the same synthetic route is used by the different suppliers of the same starting material and starting materials comply with the same specifications regardless of the supplier.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The critical quality attributes (CQAs) of lumacaftor are: appearance, identification, assay, organic impurities, inorganic impurities, residual solvents, physical form and particle size. As part of the enhanced approach to pharmaceutical development, the manufacturing process of lumacaftor was risk-assessed to identify those material attributes and process parameters affecting the CQAs. The control strategy for the starting materials, intermediates, drug substance and in-process controls were taken into account during the risk assessment. The results of this study indicated that all lumacaftor CQAs, except identification, are potentially impacted by the process.

The manufacturing process has been developed using a combination of conventional univariate studies and design of experiment (DOE) studies. Based on these studies design spaces were developed for some steps of the synthesis. The design space verification and proposed lifecycle management have been discussed in detail and are based on a risk assessment of potential scale dependent phenomena for each step along with the control strategy (design space) demonstrated during development studies. The design spaces have therefore been verified for commercial scale. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Detailed studies on the potential and observed organic impurities in lumacaftor active substance originated from starting materials, the manufacturing process and degradation processes have been presented. The fate of these impurities has also been studied by spiking experiments and purging studies, demonstrating that their level is acceptable.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Lumacaftor active substance is packaged inside a low density polyethylene (LDPE) bag secured with an appropriate closure, placed inside a second LDPE bag and secured appropriately. These closed LDPE bags are placed into a secondary container for storage and shipping. The LDPE is compliant with EU Regulation 1183/2012, and the European Pharmacopoeia Monograph 3.1.3 “Polyolefins”.

Specification

The control strategy for lumacaftor consists of the specifications of the active substance starting materials, reagents and solvents, the active substance synthesis design spaces, the in-process controls and the active substance specification.

The active substance specification includes tests for: appearance (visual inspection), identification (IR), physical form (XRPD), particle size (laser diffraction), assay (HPLC), organic impurities (HPLC), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.) and residual solvents (HS-GC).

The omission of water content, formic acid and microbial testing from the active substance specification has been adequately justified.

The analytical methods used have been adequately described and any non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data on 10 pilot scale and 3 commercial scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 12 months under long term conditions at 25 °C / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The parameters tested were: appearance, assay, organic impurities, water content (KF), microbial limits and water activity.

The stability data presented show that lumacaftor is stable when packaged in the intended container closure system under all storage conditions. No trends or out of specification results were observed.

Photostability testing following the ICH guideline Q1B was performed on one pilot scale batch. Samples were tested for appearance, assay, organic impurities, physical form and water content. This study confirmed that lumacaftor is photostable and does not require light protective packaging.

Forced degradation studies were also conducted on one batch. Stress conditions included exposure to heat, humidity, treatment under acidic, basic, neutral and oxidative conditions. Samples were tested for assay and organic impurities. Degradation was observed under basic and oxidative conditions. None of the degradation products observed under these stress conditions were found at or above the reporting threshold when the active substance was packaged and stored according to label instructions. No degradation was observed when lumacaftor was exposed to any of the other stress conditions. The results from these studies confirmed the stability indicating nature of the proposed commercial HPLC method for assay and organic impurities.

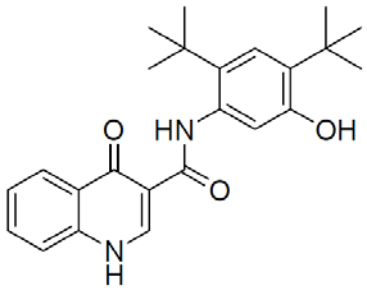
Overall, the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The proposed re-test period for lumacaftor active substance of 24 months when stored in the intended container closure system at not more than 25°C with excursions to 30°C is supported by the data presented.

Ivacaftor

The information provided on ivacaftor in support of this MAA is in line with that provided for Kalydeco (EMEA/H/C/002494), approved in 2012.

General information

The chemical name of ivacaftor is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide and has the following structure:



Molecular formula: $C_{24}H_{28}N_2O_3$ Molecular weight: 392.49 $gmol^{-1}$

Ivacaftor has a non-chiral molecular structure.

The structure of ivacaftor has been confirmed by elemental analysis, ^{1}H-, ^{13}C- and two dimensional NMR spectroscopy, UV-Visible spectroscopy, mass spectrometry, and crystallographic analysis.

The active substance is a white to off-white crystalline slightly hygroscopic solid which is practically insoluble in water and buffers with pH 1.0-7.0, slightly soluble in ethanol, methanol and acetone and soluble in 2-methyl tetrahydrofuran.

Multiple polymorphic forms have been identified for ivacaftor. The active substance produced by the proposed manufacturing process consists of a mixture of two major crystalline neat polymorphic forms, Form B and Form C. The control of the final isolation and drying conditions ensures that mixtures of the neat crystalline forms B and C are consistently produced. Nevertheless, the polymorphic form of ivacaftor during the synthesis of the active substance is not a CQA since during the manufacture of the drug product, ivacaftor is fully dissolved in a spray-drying solvent system to provide an amorphous intermediate, which is then converted to the final drug product. Therefore ivacaftor's physical form is only a CQA for ivacaftor SDD (spray dried dispersion) and the final tablets, since it is critical to maintain the amorphous form to ensure bioavailability.

Manufacture, characterisation and process controls

A Quality by Design (QbD) approach was also used for the development of ivacaftor. The manufacturing process consists of four main steps using commercially available well defined starting materials with acceptable specifications. The synthetic routes for the starting materials have been described in detail and all potential related impurities or degradation products have been described and characterized. There are different suppliers for each starting material. However, the same synthetic route is used by the

different suppliers of the same starting material. Description of the manufacturing process of the active substance including the in-process controls is adequate.

A QbD approach has also been used in product and process development of ivacaftor. For the active substance synthesis, a combination of multivariate analyses and range-finding studies was used to define a design space for each step (namely, coupling, methanololysis, form conversion/crystallization and drying). All parameters with a potential impact on CQAs of the active substance were identified and thoroughly investigated. The applicant has proposed a combination of proven acceptable ranges (PARs) and design spaces for the manufacturing process of the active substance.

Although the design spaces were developed at small laboratory scales, a design space verification protocol providing demonstration of the risk of scale dependence of the parameters which define each design space was submitted. The robustness of the process has been confirmed with the manufacture of fifteen large-scale batches of ivacaftor drug substance, which have consistently met the acceptance criteria for all drug substance CQAs. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.
Ivacaftor drug substance is packaged inside a low density polyethylene (LDPE) bag and secured with an appropriate closure (twist tie or equivalent). The bag is then placed inside a second LDPE bag and secured appropriately; the closed LDPE bags are placed into a secondary container suitable for storage and shipping. The LDPE is compliant with the Directive 2002/72/EC and the European Pharmacopoeia Monograph 3.1.3 “Polyolefins”.

Specification

The active substance specification includes tests for appearance (visual inspection), identification (FTIR), assay (HPLC), related substances (HPLC), acetamide (GC-MS), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.) and residual solvents (GC).
A detailed study on the potential, theoretical and observed organic impurities has been presented. Impurity limits in the specification are justified and found safe. The limit proposed for acetamide (hydrolysis by-product of the process solvent acetonitrile) in the active substance has been established according to the Guideline on the Limits of Genotoxic Impurities.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP requirements.

Results of analysis of sixteen commercial scale batches of the active substance were provided. Compliance with the specification was demonstrated.

Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturers stored in the intended commercial package for 18 months under long term conditions at 30 °C / 65% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided. This data were supplemented with long term stability data for up to 60 months during the evaluation procedure.

The following parameters were tested: appearance, assay, related substances, water content, physical form, microbial limits and water activity. The analytical methods used were the same as for release, with the addition of XRPD for physical form determination, and were stability indicating.

No trends in the assay or water content data were observed through 18 months of storage at 30 °C / 65% RH. Although a statistically significant trend was observed for these parameters on samples stored at 40 °C / 75% RH through 6 months, all results remained well within the commercial specification acceptance

limit. The XRPD stability data show that ivacaftor remains crystalline at all test points under all storage conditions. In addition, data presented show no increase on water activity levels and no change in microbial content after storage for 12 months at 30 °C /6 5% RH. Thus, all tested parameters remained within the commercial specification acceptance limits.

Ivacaftor active substance was also subjected to stress conditions including exposure to heat and heat combined with humidity for up to 21 days, treatment under acidic, basic, neutral and oxidative conditions for up to 14 days, exposure to pH 4 and pH 7 for up to 7 days and exposure to light conforming to ICH Q1B option 2 requirements. Ivacaftor was found to be the least stable under basic conditions and when in solution exposed to light. No degradation was observed when ivacaftor was exposed to the other stress conditions. Analysis of the stressed samples confirmed that the commercial HPLC method for assay and organic impurities determination in ivacaftor active substance is stability indicating.

In addition, photostability testing following the ICH guideline Q1B was performed on one batch. The data, showing no changes in the fully exposed test sample and the covered control, confirm that ivacaftor drug substance is photostable and therefore does not require light protective packaging.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 30 months in the proposed container closure system.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Orkambi is a fixed dose combination (FDC) pink immediate-release film-coated tablet for oral administration containing 200 mg of lumacaftor and 125 mg of ivacaftor as active substances.

Lumacaftor active substance is provided as a crystalline solid. Ivacaftor active substance is provided as an amorphous SDD intermediate. This is due to the fact that, although ivacaftor is a stable crystalline material of high purity with well characterized physical and chemical properties, it is practically insoluble in aqueous media (< 0.05 µg/mL) and has low bioavailability. As a result, several approaches to obtain materials with better aqueous solubility were explored. Spray drying was selected as the preferred process to produce an ivacaftor solid dispersion with suitable properties for direct compression.

Product and manufacturing process development was conducted under a QbD paradigm.

The quality target product profile (QTPP) was to develop safe, efficacious and bioavailable immediate-release fixed-dose combination tablets containing 200 mg of lumacaftor and 125 mg of ivacaftor, suitable for oral administration, easily distinguishable from other medications consumed by the intended patient population, with a 24 month shelf-life at room temperature and packaged in blisters and with a posology of two tablets every 12 hours.

Following the definition of the QTPP, the CQAs for the lumacaftor active substance, ivacaftor SDD and the lumacaftor/ivacaftor FDC tablet were identified. As described in section 1.1.2, the CQAs of lumacaftor drug substance are: appearance, identification, assay, organic impurities, inorganic impurities, particle size, residual solvents and physical form. The CQAs for ivacaftor SDD are: appearance, identification, assay, residual solvents, physical form, degradation products and water content. The CQAs for the FDC tablets are: appearance, identification, assay, physical form, degradation products, water content, dissolution, content uniformity and microbial attributes.

Subsequently, as part of the QbD approach, an initial risk assessment was performed on the drug substance and the tablets to determine which materials and process steps could potentially impact the CQAs. This risk assessment and prior knowledge were then used to design multivariate experiments to

evaluate main effects and interactions and determine criticality. Data from these studies were analysed to determine the design spaces that ensure all CQAs are within acceptance limits. Once the design spaces were finalized, process models which describe them or which were used as part of the control strategy were finalized.

The process knowledge gained throughout QbD development formed the basis of the overall product control strategies for the active substances and the finished product. The control strategy includes control of input material attributes, critical process parameters, in-process controls, and product specifications.

A rationale has been provided for the choice and level of each excipient, including the non-functional film coat and printing ink. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The compendial excipients comply with the Ph. Eur requirements. Hypromellose acetate succinate (HPMCAS) complies with the USP/NF monograph and meets the requirements of the Ph. Eur. substances for pharmaceutical use and ICH Q3C requirements. Opadry II pink and Opacode black are non-compendial excipients mixtures wherein the individual components meet the appropriate requirements of the Ph. Eur. In view of the continuous manufacturing process, the excipients were risk assessed for potential impact on the drug product CQAs and information on the control of the excipients used, in addition to the pharmacopoeial requirements has been presented. This included a discussion on the need to implement functionality-related tests. Overall, the excipients and levels chosen for the commercial formulations demonstrate acceptable process characteristics and product performance across the design space.

Several studies were also conducted to examine and demonstrate the chemical and physical compatibility of the lumacaftor drug substance and ivacaftor SDD with the tablet excipients as well as with each other.

Since incompatibilities were not detected between the two drug substances, a mono-layer tablet formulation was developed. A conventional formulation development was conducted using well known excipients and standard manufacturing processes (wet granulation, compression and coating).

Different lumacaftor/ivacaftor formulations have been used throughout the clinical development program. Initial clinical studies were conducted with lumacaftor only and included a lumacaftor oral water based suspension formulation used in early Phase 1 clinical studies and a lumacaftor capsule formulation used in subsequent Phase 1 and early Phase 2 studies. Clinical development then moved to combination therapy and ivacaftor was added to the regimen. Early Phase 1/2 clinical studies used individual lumacaftor and ivacaftor tablets. Later on, to enhance patient safety and compliance, a FDC tablet containing 200 mg lumacaftor and 125 mg ivacaftor as SDD was developed. A bioavailability study (Study 007) was completed that supported the use of FDC tablets in Phase 3 clinical studies. The Phase 3 pivotal studies included 2 dosing regimens and used both a lumacaftor/ivacaftor FDC tablet, 200/125 mg and a lumacaftor/ivacaftor FDC tablet, 200/83 mg. Additionally, in the Phase 3 regimen that utilized the lumacaftor/ivacaftor FDC tablet, 200/83 mg, an individual ivacaftor, 125 mg tablet was also dosed. From these studies, the formulation selected for commercial use was the 200mg/125 mg FDC tablet.

The final commercial FDC tablet formulation is identical to the 200 mg/125 tablets used in clinical trials with the exception of the printing in the film-coat, and the presence of traces of carnauba wax in tablets manufactured at one of the proposed manufacturing sites. It has been justified that the addition of the print or the presence of carnauba wax do not impact dissolution.

Two independent *in vitro* dissolution methods, one for each active ingredient, were developed for testing the lumacaftor/ivacaftor FDC tablets. During the method development process, parameters were carefully selected to ensure that each method is discriminatory and suitable for its intended use. Both dissolution methods have shown the ability to discriminate against meaningful manufacturing variations

and are considered suitable for their intended use as the primary release and stability quality control methods for lumacaftor/ivacaftor FDC tablets.

The primary packaging is a blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminium foil lidding. The material complies with the current European Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03), the Directive 2002/72/EC and Regulation No 10/2011 and/or the relevant European Pharmacopoeia Monograph. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacture of Orkambi is a two-stage process.

In the first stage, crystalline ivacaftor drug substance is dissolved with a polymer and a surfactant in the process solvents, then spray dried to form a powder, which undergoes secondary drying to further remove process solvents to acceptable limits. This results in an amorphous spray-dried dispersion drug product intermediate (SDD) which is a free flowing, compressible powder.

The second stage, which involves the manufacture of the FDC tablets, consists of seven steps: intra-granular blending, twin screw wet granulation, fluid bed drying and milling, extra-granular blending, compression, film coating, and printing.

Three different manufacturing sites which use a continuous wet granulation process, but with slightly different systems and PAT capabilities, are proposed for the manufacture of the FDC tablets. One of the sites employs a twin screw granulator fed by a batch blend, followed by stand-alone batch fluid bed drying. The second site has a continuous tableting line which operates in a continuous mode from granulation to compression, with initial blending and film coating performed in batch mode. The third site uses a system which operates in continuous mode from individual components feeding to film-coated tablets and is enabled with real-time release testing (RTRT) capability.

The impact of line rate was studied as part of the design space development experiments. The automatic adjustments the system requires are well within the design space limits of line rate.

Spectroscopic and non-spectroscopic PAT are used for in-process controls. Spectroscopic and non-spectroscopic PAT measurements are implemented for real time release testing (RTRT) at one of the proposed manufacturing sites , as described under the product specification section.

Design spaces have been proposed for the several steps of the manufacturing process of the SDD (spray drying) and the FDC tablets: intra-granular blending, blending, twin screw wet granulation, fluid bed drying and milling, extra-granular blending, compression, film coating, and printing.

The design spaces have been developed at the commercial scale manufacturing equipment. Confirmation experiments to demonstrate the validity of the models developed were conducted. Therefore, the available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Process validation of the ivacaftor SDD intermediate manufacturing process has been completed on three consecutive commercial scale batches.

For the manufacture of the FDC tablets, traditional process validation, in accordance with the CHMP Guideline on process validation for finished products (EMA/CHMP/QWP/BWP/70278/2012-Rev1), will be conducted at the three proposed manufacturing sites post-approval in line with the submitted process validation scheme.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form.

For the manufacturing sites on which the finished product is released on the market through traditional final product release testing. They include: appearance (visual), identification (IR), assay (HPLC), dissolution (Ph. Eur.), water content (KF), uniformity of dosage units (HPLC), physical form of lumacaftor and ivacaftor (XRPD) and microbial limits (Ph. Eur.).

For the manufacturing site on which real time release testing will be employed, the finished product specification includes: identification (Raman), assay (NIR on blend, core tablet weight), dissolution (high impact model), water content (NIR on blend), content uniformity (NIR on blend, core tablet weight), physical form (Raman) and microbial limits (Ph. Eur.).

In line with the CHMP Guideline on Real Time Release Testing (EMA/CHMP/QWP/811210/2009-Rev1), the relationship between RTRT and end product testing and associated specification has been supported by comparative data at commercial scale (parallel testing), which will continue post-approval.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The NIR and Raman methods proposed have been developed and validated in line with EMA's guideline on the use of near infrared spectroscopy by the Pharmaceutical Industry and the data requirements for new submissions and variations (EMEA/CHMP/CVMP/QWP/17760/2009 Rev2). The quality profile of all reference materials has been correctly established.

Development and validation of the high impact dissolution rate model for ivacaftor and lumacaftor have been adequately presented. The capability of the RTRT dissolution models to properly characterize dissolution performance of a batch has been demonstrated by the results obtained from the design space confirmation runs on that facility.

The discriminatory power of the dissolution model has been demonstrated.

Batch analysis results have been provided on three pilot and five commercial scale batches of ivacaftor SDD, and eleven pilot and three commercial scale batches of film-coated tablets manufactured at the proposed manufacturing sites. They confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on one pilot scale and two commercial scale batches of ivacaftor SDD stored under long term conditions for 12 months (2 batches) or 24 months (1 batch) at 30 ºC / 65% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of ivacaftor SDD are identical to those proposed for marketing and were packed in primary packaging representative of the one proposed for marketing (single tied off LDPE bag within a heat-sealed foil laminate bag that contains a 5% w/w load of molecular sieve desiccant).

Supporting stability data from three additional pilot scale batches stored for 18 months under long term conditions and for 6 months at accelerated conditions were also provided.

Samples were tested for appearance, water content, assay, degradation products, physical form, microbial limits and water activity.

The primary stability lots showed no changes over time for any of the attributes evaluated. The stability data from the supporting lots showed an increase in water content along with a corresponding decrease in assay for all storage conditions due to the samples being packaged without moisture protection (double polyethylene bags without desiccant and without an outer heat-sealed foil laminate bag). There were no other changes in the supporting stability lots under all storage conditions.

Photostability testing as per ICH Q1B, Option 2, was performed on one of the supporting stability batches. The photostability data showed no changes in the fully exposed test sample and the covered control, and confirmed that ivacaftor SDD does not require light protective packaging.

Based on available stability data, the expiry period for ivacaftor SDD of 24 months when stored in the proposed container closure system is acceptable.

With regards to the finished product, stability data on three formal stability batches of lumacaftor/ivacactor FDC tablets 200/125 mg manufactured at each of the three proposed manufactured sites stored under long term conditions at 25 ºC / 60% RH or intermediate conditions at 30 ºC / 65% RH for up to 24 months were provided. Data from three batches from one site stored for six months under accelerated conditions at 40 ºC / 75% RH were also submitted. The batches of lumcaftor/ivacaftor FDC tablets are identical to those proposed for marketing and were packed in primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, water content, physical form, microbial limits and water activity. The analytical procedures used are stability indicating

All results met the acceptance criteria for all the attributes evaluated. Although a small increase in water content was observed, it had no impact on the tablet physical and chemical properties. Additionally, a slowsdown in initial dissolution was observed, but it reached a plateau over time and all results met the specification limits. Overall, the stability data show that the drug product is stable when packaged in the configuration proposed for commercial distribution under all storage conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay and degradation products. The data showed no changes in the fully exposed test samples and the covered controls, demonstrating that the lumacaftor/ivacaftor tablets do not require light protective packaging.

Based on available stability data, the shelf-life of 24 months without any storage requirements as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner.

The applicant has applied QbD principles in the development of the active substances and finished product and their manufacturing processes. Design spaces have been proposed for several steps in the manufacture of the active substances and finished product. The design spaces have been adequately verified.

The manufacture of the FDC tablets uses a continuous wet granulation process. Additional steps (e.g. intra-granular and extra-granular blending, granulation, drying, milling, compression, film-coating or printing) are also performed in a continuous mode in some of the proposed manufacturing sites.

Following this QbD approach, a real time release testing strategy has been proposed for the site which operates in full continuous mode from individual components to film-coated tablets.

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Cystic fibrosis (CF) is caused by mutations in the CFTR gene resulting in absent or deficient function of the CFTR protein at the cell surface. CFTR is an ATP-gated chloride channel located in the epithelia of a number of organs, including lung, pancreas, intestinal tract and liver, where it regulates salt and water absorption and secretion. Loss of chloride transport results in the accumulation of thick, sticky mucus on the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption and reproductive dysfunction. Lumacaftor, also known as VX-809 or VRT-826809, is an orally bioavailable small molecule CFTR corrector designed to work in combination with ivacaftor, a CFTR potentiator. Lumacaftor increases the amount of CFTR delivered to the cell surface, and ivacaftor increases the channel gating activity of the CFTR protein at the cell surface, thereby maximising CFTR-mediated Cl- secretion.

The non-clinical data provided for the present application include in vitro pharmacodynamic studies performed with ivacaftor alone (the active substance included in Kalydeco approved by the CHMP in 2012, for which the applicant is the Marketing Authorisation Holder), with lumacaftor alone and with the FDC. No in vivo pharmacology studies were conducted. A comprehensive set of in vitro and in vivo safety pharmacology studies (rats and dogs), pharmacokinetics studies (rats, dogs and monkeys), and toxicology studies (mice, rats, rabbits and dogs) were conducted with ivacaftor and lumacaftor alone. Genotoxicity, carcinogenicity, reproductive and developmental toxicity studies were not performed with the FDC as the studies conducted in these specific areas on each individual entity were considered adequate for assessment of the risk associated with co-administration.

All safety pharmacology, toxicity, and toxicokinetic studies considered pivotal to safety assessment were conducted in compliance with Good Laboratory Practice (GLP) regulations with any exceptions duly noted and were conducted in Association for Assessment and Accreditation of Laboratory Animal Care

International (AAALAC) accredited facilities as claimed by the applicant.

Since the applicant is already the MAH for ivacaftor, some of the development studies of this FDC will be overlapping with the development of ivacaftor as monotherapy.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The following primary PD in vitro studies with lumacaftor and ivacaftor were carried out:

LUMACAFTOR

Type of Study / Description	GLP[a]	Test System	Method of Administration
Effects on CFTR-Mediated Chloride Secretion	No	HBE cells	In vitro
Determination of the Efficacy Criteria for CFTR Modulators Based on Genotype-to-Clinical Phenotype Correlations in Cystic Fibrosis Subjects	No	Multiple published studies	NA
Effects of VRT-826809 on Protein Conformation, Trafficking and Channel Gating of ΔF508-CFTR	No	HBE cells HEK-293 cells	In vitro
Validation of Primary Human Bronchial Epithelia Cultures to Evaluate the Pharmacological Action of CFTR Modulators	No	HBE cells	No compound treatment
Effects of VX-809 on the stability of C-terminal CFTR truncations and on the covalent binding of a biologically active, radiolabeled photoactivated analog of VX-809	No	Live Sf9 cells	In vitro
Effects of VRT-0995096 on CFTR activity in cultured human bronchial epithelial isolated from the bronchi of a F508del homozygous cystic fibrosis patient	No	HBE cells	In vitro

IVACAFTOR

The non-clinical pharmacology data provided for ivacaftor were already assessed in support of the registration of Kalydeco (2012), for which the applicant is the MAH.

Type of Study / Description	GLP[a]	Test System	Method of Administration
Ion channel selectivity	No	NIH3T3, FRT, and CHL cells	In vitro
Activity on F508del-CFTR	No	NIH3T3 and FRT cells	In vitro
Activity of F508del-CFTR from homozygote	No	HBE cells and nasal polyps	In vitro
Activity on R117H-CFTR	No	FRT cells	In vitro
Activity on F508del-CFTR	No	HBE cells	In vitro
Activity on F508del/splice mutant from heterozygote	No	HBE cells	In vitro
Activity on G551D-CFTR	No	HBE and FRT cells	In vitro
Effect on multiple mutant CFTR forms	No	FRT or HBE cells	In vitro

LUMACAFTOR+IVACAFTOR combination

Type of Study / Description	GLP[a]	Test System	Method of Administration
Effects of VX-809 and VX-770 on airway surface liquid height and cilia beat frequency	No	HBE cells	In vitro
Effects of VX-770 and VX-809 combinations on F508del-CFTR function in cultured F508del/F508del-HBE	No	HBE cells	In vitro

[a] *An entry of "Yes" indicates that the study includes a GLP compliance statement.*

The in vitro pharmacological studies conducted by the applicant show that the mechanism of action of lumacaftor appears to be through facilitation of the cellular processing and trafficking of ΔF508-CFTR by partially correcting the molecular defect of ΔF508-CFTR. This leads to an increase in the amount of functional CFTR protein at the cell surface, and subsequent increased chloride transport. The gating activity of this 'corrected' ΔF508-CFTR at the cell surface can then be further potentiated by ivacaftor to enhance chloride transport, thus supporting the rationale for the co-treatment approach.

No in vivo pharmacodynamic studies were performed with lumacaftor as no validated CF animal models are available. Instead, cultured primary human bronchial epithelial (HBE) cells from patients with CF (expressing ΔF508-CFTR) were used to test the mechanism of action of lumacaftor and support its use in combination with ivacaftor for the intended therapeutic indication. This model is considered appropriate since CF HBE cells exhibit typical characteristics associated with CF lung pathogenesis, including defects in ion and fluid transport. In ΔF508-CFTR HBE cells, lumacaftor treatment increased chloride transport from a baseline of 3.4% to 13.9% of wild-type CFTR levels, with an EC_{50} of 81±19 nM. When ivacaftor was added to lumacaftor-treated cells, chloride transport was further enhanced to 25.1% of wild-type CFTR levels. Treatment with lumacaftor was required for at least 24 hours prior to chloride secretion measurements, in order to allow for de novo synthesis, processing and trafficking of 'corrected' ΔF508-CFTR to the cell surface. In support of this, little-to no response was observed on chloride transport following ivacaftor treatment in the absence of lumacaftor in HBE cells expressing ΔF508-CFTR. The physiological relevance of lumacaftor and ivacaftor-mediated correction of chloride transport was demonstrated in HBE cultures by the increase in airway surface liquid height and ciliary beat frequency, showing a normalisation of fluid secretion, and thus potentially a therapeutic benefit on mucociliary clearance in cystic fibrosis patients.

Lumacaftor was shown to bind to the MSD1 region of CFTR, and facilitate the correct folding of ΔF508-CFTR during its biogenesis in the ER. A truncated form of ΔF508-CFTR containing only the MSD1 domain was less susceptible to proteolytic digestion following treatment with lumacaftor, suggesting that CFTR was in a more stable and compact folded form. Lumacaftor increased the efficiency of ΔF508-CFTR export from the ER, and cell surface stability of lumacaftor-corrected ΔF508-CFTR was also shown to be improved, suggesting a reduced susceptibility to lysosomal degradation. Patch-clamp experiments confirmed that lumacaftor alone or in combination with ivacaftor increased the channel open probability (up to 111±21% of normal CFTR when in combination with ivacaftor) compared to uncorrected ΔF508-CFTR. Given that the gating activity of lumacaftor-corrected CFTR is approximately 50% of normal CFTR, it does not appear that lumacaftor completely restores normal protein function.

Recent published evidence from two separate academic groups suggested that prolonged ivacaftor treatment (24-48 hours in primary human bronchial epithelial cells) may adversely affect the function of lumacaftor-corrected Δ508-CFTR, by diminishing the folding efficacy and metabolic stability, ultimately resulting in significantly reduced functional expression at the cell surface (Cholon *et al*, Sci Transl Med 6(246) 2014 and Veit *et al* Sci Transl Med 6(246) 2014). These *in vitro* data indicate that chronic

treatment with ivacaftor may be detrimental for the restoration of Δ508-CFTR function, and raises questions regarding the proposed benefits of the ivacaftor/lumacaftor combination. It is noted that the definition of 'chronic' in the *in vitro* setting in these published studies is no longer than 48 hours. The relevance of this time point, particularly in the light of the demonstrated clinical efficacy (although modest) over much longer duration, is questionable. After extensive review of these data a clinical impact on the pharmacological mechanism of action of the ivacaftor/lumacaftor combination is considered not being likely.

Secondary pharmacodynamic studies

Lumacaftor was highly selective when tested in a panel of 168 in vitro receptor, channel and enzyme radioligand assays. Only relatively weak antagonism (reversal of TXA2 agonist-induced contractile response in rat aortic rings) was demonstrated at the TXA2 receptor. In addition, lumacaftor was highly selective against correction of CFTR trafficking relative to a range of other misfolded and wild-type proteins. Lumacaftor was not considered to be a hERG channel blocker, since the maximum soluble concentration (4.6 μM) inhibited hERG potassium current by only 0.2±0.2%, which was not statistically significant compared to controls.

With respect to ivacaftor secondary and safety pharmacology, only two targets were inhibited with nanomolar potency out of 140 enzymes and receptors tested: the monoamine transporter and serotonin 5-HT2C. However, due to low blood-brain-penetration, ivacaftor is unlikely to interact with these CNS targets in humans. In addition, ivacaftor inhibited only CaV1.2 (IC_{50} = 1.3 μM) and KV1.5 (IC_{50} = 3.4 μM) channels with moderate potency. Ivacaftor caused hERG inhibition with an IC_{15} of 5.5 μM, and was therefore not considered a potent hERG inhibitor. Any risk of off-target effects from ivacaftor in humans at therapeutic dose levels and exposures is minimal, since ivacaftor is highly plasma protein bound across all species, and the free plasma concentration at therapeutic dose will be low (approximately 4 nM). Finally, ivacaftor produced an inhibition of gastric emptying and gastrointestinal transit in male rats at high doses (≥500 mg/kg). However, no adverse effects on the GI system were noted in repeat dose toxicity studies in rats and dogs.

Based on the highly selective nature of lumacaftor in the secondary and safety pharmacology studies, any detrimental pharmacodynamics drug interaction with ivacaftor does not seem likely.

Safety pharmacology programme

In safety pharmacology studies, lumacaftor did not produce any effects on the CNS and respiratory systems in rats at single oral doses of up to 1000 mg/kg. In addition, lumacaftor had no effect on gastric motility when tested up to 1000 mg/kg in rats. There were no effects of lumacaftor on cardiovascular (blood pressure, heart rate and ECG) parameters in dogs, when tested up to 200 mg/kg, also confirming the absence of a physiological translation of the TXA2 receptor antagonistic effect.

Pharmacodynamic drug interactions

In vitro pharmacodynamic interaction studies of lumacaftor and ivacaftor were conducted earlier. These studies support the proposed combination of lumacaftor and ivacaftor, with lumacaftor partially correcting the molecular defect of ΔF508-CFTR to increase the amount of functional ΔF508-CFTR at the cell surface, with ivacaftor further enhancing the chloride transport of the cell surface ΔF508-CFTR. The justification for the therapeutic combination of lumacaftor and ivacaftor based in the presented pharmacodynamic studies is considered adequate to the CHMP.

2.3.3. Pharmacokinetics

Absorption of lumacaftor and ivacaftor in mice, rats, rabbits and dogs was rapid, and bioavailability ranged from 30% to 100%. The apparent permeability of lumacaftor and ivacaftor in Caco-2 cell monolayer is high, which may have contributed to a high oral bioavailability. Neither lumacaftor nor ivacaftor were substrates for the efflux transporter P-gp.

Lumacaftor is considered a highly permeable compound, and this finding is confirmed by results from two studies performed under the same experimental condition and with the same concentration of 10 µM.

Systemic exposures to lumacaftor and ivacaftor in combination studies in rats and dogs were largely similar to the exposures achieved when the compounds were dosed individually. However, in rats when comparing the 28-day toxicity study conducted with lumacaftor alone, lumacaftor exposure in the 300 and 1000 mg/kg dose groups included in both studies was generally higher (>2-fold) in the combination toxicity study in both sexes. In addition, lumacaftor exposure in male rats in the 3 month combination toxicity study also appeared higher than in the 3 month study with lumacaftor alone. The applicant considered that any differences in lumacaftor exposure were likely a result from inherent variation across studies. Besides, pharmacokinetic studies in rats confirmed the absence of interaction between lumacaftor and ivacaftor. A dose-proportional increase in exposure was observed when lumacaftor and ivacaftor were dosed at lower doses. However, at higher doses including those explored in toxicity studies, exposure was generally less than dose proportional. No significant gender differences were observed; no evidence of accumulation of lumacaftor after repeated exposure was seen. Ivacaftor exposures were higher at steady-state compared to single dose exposures.

Protein binding of lumacaftor and ivacaftor is high (>98%) in mouse, rat, rabbit, dog, and human plasma and primarily bound to HSA in isolated human plasma protein components. Both lumacaftor and ivacaftor were rapidly distributed across most tissues in rats. Gastrointestinal (GI) tissues showed highest exposure, followed by liver and kidney. Lowest exposures were noted in the brain, eyes and testes. Neither lumacaftor nor ivacaftor binds to melanin containing tissues (skin and/or eyes). Placental transfer of lumacaftor was confirmed in rats and rabbits, whith low levels of radioactivity detected across a range of foetal tissues. For ivacaftor, placental transfer was limited. In vitro studies demonstrated that warfarin was able to displace lumacaftor from plasma protein binding to a small degree, increasing the fraction of unbound lumacaftor from 0.05% to 0.1%, suggesting a potential for plasma protein binding-related drug-drug interactions. However, this small change in fraction unbound was not considered to influence clinical exposure.

Lumacaftor metabolism primarily involved oxidation (M1) and/or glucuronidation (M2), but the majority of lumacaftor was excreted unchanged. M28-lumacaftor was a major human metabolite after single doses, and was not detected in non-clinical species. However, after repeated doses humans, M28-lumacaftor accounted for less than 10% of parent, and was therefore considered to be a minor human disproportionate metabolite. M22-lumacaftor was a major excretory metabolite of lumacaftor. The M28-lumacaftor metabolite was stated to be pharmacologically inactive. The major ivacaftor metabolism pathway was oxidation to M1- and M6-ivacaftor, and only a small proportion was excreted as unchanged parent. M1-ivacaftor had a much lower (1/6th) pharmacological potency than ivacaftor, and M6-ivacaftor was pharmacologically inactive. Lumacaftor and ivacaftor are both substrates of CYP3A4; however, sensitivity to CYP3A4 metabolism was much greater for ivacaftor than lumacaftor. Lumacaftor also activates PXR, which may cause downstream effect on induction of PXR-dependent CYP enzymes, including CYP3A4. Neither lumacaftor nor ivacaftor are substrates for uptake transporters OATP1B1 and OATP1B3.

Based on in vitro studies, lumacaftor and ivacaftor both have potential to inhibit P-gp, but not expected to inhibit OATP1B1 or OATP1B3. The effect of lumacaftor and ivacaftor on other transporters (including

OAT1, OAT3, OCT2, OCT1, BCRP or BSEP) was not initially described. The Applicant will conduct studies to evaluate the inhibition of BCRP, but considered that evaluation of BSEP was not necessary, due to the absence of data suggesting reduced bile salt secretion and cholestasis. In addition, due to the low renal clearance of lumacaftor, the Applicant considered that evaluation of OAT and OCT was not necessary. However, this was not accepted by the CHMP, and the Applicant agreed to evaluate potential inhibition of OAT1, OAT3, OCT1 and OCT2 as a post-authorisation measure.

Faecal and biliary excretion was the primary route of elimination for both lumacaftor and ivacaftor. Lumacaftor was excreted primarily as unchanged parent; whereas, ivacaftor was eliminated as polar oxidative metabolites. Since lumacaftor is eliminated predominantly unchanged in the faeces, biliary secretion by transporters may be involved, and these should be identified and possible polymorphisms considered. The Applicant has agreed to complete studies to evaluate whether lumacaftor is a substrate for BCRP and MRP2 as a post-authorisation measure. Both lumacaftor and ivacaftor were excreted in the milk of lactating rats.

In summary, the CHMP concluded that the in vitro studies suggest that lumacaftor and ivacaftor and M1-ivacaftor may have pharmacokinetic interactions with other drugs that are CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A or P-gp substrates. These potential interactions are adequately described in the SmPC.

2.3.4. Toxicology

The toxicology programme of LUM/IVA FDC has been performed according to the ICH/CHMP relevant guidelines and was supported by studies: i) conducted with lumacaftor and its minor but disproportionate and pharmacologically inactive human metabolite M28 (evaluated independently); ii) conducted with ivacaftor taking into account its major circulating metabolites in all species studied i.e. M1 metabolite (1/6th of the potency of ivacaftor) and M6 metabolite (pharmacologically inactive); iii) conducted with the combination LUM/IVA.

In all studies, the products were administered by oral (gavage) route, which is intended for human use. All pivotal studies were in compliance with GLP regulations. Based on the primary pharmacology of lumacaftor and ivacaftor, rats and dogs were selected as relevant species for the toxicological assessment of the drug.

Single dose toxicity

Single-dose studies conducted in mice and rats up to 2000 mg/kg suggest that the acute oral toxicity of lumacaftor is of low order. In mice, the MTD and NOAEL were ≥ 2000 mg/kg, in rats both the NOAEL and NOEL were 1000 mg/kg, and the MTD in rats was ≥ 2000 mg/kg, based on 100% survival rate. Dose-based safety margins relative to the intended human therapeutic dose of lumacaftor in the FDC (800 mg total daily) were 10 and 20-fold higher (for mice and rats, respectively) at the MTD, based on the surface-area extrapolation method and assuming a 50 kg human body weight. The ivacaftor MTD were 2000 mg/kg in mice and 500 mg/kg in rats. Dose-based safety margins relative to the intended human therapeutic dose of ivacaftor in the FDC (500 mg total daily) were 8- and 16-fold higher in rats and mice respectively at the MTD, based on the surface-area extrapolation method and assuming a 50 kg human body weight.

The lack of LUM/IVA combination single-dose oral toxicity studies is acceptable to the CHMP, since the studies conducted for each product showed no evidence of potential for additive or synergistic interaction and are adequate to assess the acute toxicity safety risk associated with co-administration. Additional in vivo studies are not needed or justified.

Repeat dose toxicity

Lumacaftor repeat dose toxicity in mice was evaluated in two studies of 4-week duration (Tg.rasH2 mice;VX-809-TX023) and 13-week duration (CD 1 mice; VX-809-TX015). In Tg.rasH2 mice, the MTD was 4000 mg/kg/day based on mortality and significant effects on body weight and body weight gain. This dose produced high systemic exposure, as evidenced by steady state AUC 0-24h value of 2260 µg.h/mL in males, which is 5.7-fold greater than that observed in humans with administration of LUM 800 mg/day (396 µg.h/mL). In CD1 mice the MTD was 2000 mg/kg/day based on mortality. This dose produced a systemic exposure (AUC 0-24h 2490 µg.h/mL in males) - 5.9-fold greater than that observed in humans with the lumacaftor dose of the FDC.

In the 13-week study in rats, the lumacaftor NOAEL is 2000 mg/kg/day. Liver, spleen and thymus organ weights (absolute and/or relative organ weight changes, irreversible for tyhymus) were increased at 2000 mg/kg/day, and microscopic treatment-related findings were present in the liver (centrilobular hypertrophy) and spleen (increased extramedullary hematopoiesis). The applicant considered these findings not to be adverse under the conditions of this study, considering liver alterations as adaptive phenomena, spleen increases as secondary to haematological changes and irreversible thymus weight decreased as stress-related and/or due to body weight loss. These justifications are acceptable to the CHMP, taking into account that these findings were observed after 26 week duration treatment up to 1000/25 mg/kg/day of LUM/M28LUM, suggesting an adaption to the LUM administration in rats.

In dogs, the observed effects, although similar to those seen in rats, appeared to be more frequent and intense. The main concern relates to findings observed in 13 week duration study in one male showing hematopoietic cellularity of the bone marrow moderate in the sternum and marked in the femur that could indicate potential detrimental effects on bone marrow. Moreover, in all dog studies, the decreases in haemoglobin, haematocrit and red blood cells (seen in both genders at almost all doses) were not associated with an increase in the number of reticulocytes, suggesting an inadequate response to the bone marrow, conversely to what happened in the rat, in which decreases in erythrocytic parameters appear regenerative. However, it is recognised that the bone marrow effects were observed at doses higher than the MTD. The decreased cellularity of the bone marrow was fully reverted after the one month-recovery period, furthermore, these findings do not appear to translate into the clinical setting as no significant effects on erythrocytic parameters were demonstrated in the Phase 3 study. Based on bone marrow finding besides mortality, clinical signs and significant body weight decrement with the lumacaftor dose of 1000 mg/kg/day exceeded the MTD in this species after 13 week duration treatment; therefore the NOAEL is considered 500 mg/kg/day.

In 26-52 week duration studies, dose-related increase in absolute (up to 24%) and relative liver weights in females at ≥ 125 mg/kg/day and in males at ≥ 250 mg/kg/day were induced after 12 months treatments. This correlates with ALT increase at dose ≥250 mg/kg/day, without any macroscopic or microscopic findings and fully reversible. The NOAEL is considered to bw 500 mg/kg, corresponding to the exposure at the steady state of AUC0-24hr 515/429 µg.hr/mL (M/F) and Cmax 61.3/ 56.0 µg/mL (M/F).

With regards to the thymus alterations, it is recognised that thymus undergoes involution characterised by decrease in cellularity, depending on diet, age, sex, strain and species of animals being tested. Thymus involution is difficult to differentiate by thymus atrophy induced by inadequate nutrition, stress, or toxicity (Pearse, 2006). The histological appearance of the thymus under these varied conditions is similar, since the endpoint is the reduction in cortical lymphocytes, and shrinkage of the thymus lobules (Schuurman et al., 1994), and factors such as stress and toxicity can simultaneously be superimposed on the normal ageing process of lymphocyte reduction. On these bases, the applicant's opinion that the lymphoid depletion was at least partially due to an indirect effect, secondary to stress and/or weight loss is scientifically sustained.

The LUM/IVA co-administration in dogs for 4 weeks induced a decrease in thymus weights (-37, 59, 58 and 51% in males; -28, 29, 43 and 48% in females for doses > 300/ 5mg/kg/day LUM/IVA) and enhance lymphoid depletion as compared to controls. This is also associated with a lympahocyte and eosinophil reduction starting from a dose higher than 300/15 mg/kg/day LUM/IVA. Since no thymus findings are raised during assessment for ivacaftor MAA (filed and owned by the same applicant), data obtained from co-administration studies suggest that the exacerbation of thymus involution may be due to LUM only. In addition, 6 month carcinogenicity study in Tg.rasH2 mice showed that 2 out of 50 mice developed thymomas. In light of this, the Applicant has thoroughly reviewed the available data on thymus alterations and further corroborated that the correlation between stress response and the concurrent thymus changes is consistent with guidance for identifying stress responses in routine toxicology studies, as issued by the Society for Toxicologic Pathology Regulatory Policy Committee. Moreover, the lack of effects on other lymphoid tissues does not suggest a primary effect on the immune system.

Ivacaftor target organs in rat and dog chronic toxicity studies were liver, kidney and heart. Hepatotoxicity, cardiomyopathy and nephropathy in rats are considered mainly rodent-specific phenomena. Microscopic changes associated with co-administration of lumacaftor and ivacaftor were present in glandular stomach, duodenum and kidneys in rats, and gallbladder and reproductive system in dogs. Erosion of the mucosa of the glandular stomach, graded minimal to moderate without significant inflammatory response, was observed in 4/10 animals and 14/80 animals dosed with LUM/IVA or LUM/IVA/M28LUM respectively for 4 and 13 week. Kidney basophilic and dilated tubules in rats administered LUM/IVA or LUM/IVA/M28LUM were observed mainly in males at the highest combination dose (LUM/IVA 1000/100 or IVA/LUM/M28LUM 100/1000/20mg/kg/day). The applicant attributed these effects to a non-adverse potential test article exacerbation of chronic progressive nephropathy (CPN), a known age-related, background kidney finding in rats, with higher incidence and severity seen in males than females. This hypothesis is considered reasonable and it is supported by literature (Hard and Nasir Khan, 2004). The effects were not observed after administration of LUM, but were already observed for IVA alone at doses > 50 mg/kg in chronic (6 months) study in rats, involved also rodent specific mechanism (Kalydecdo EPAR). Therefore, these could be considered class effects of the test articles, and seem confirmed by the observed degenerative /regenerative kidney tubular lesions observed in TgH2 6 month carcinogenicity study. Since the mechanism underlying the spontaneous disease process remains unknown, it would be more appropriate to consider the potential LUM/IVA exacerbation effects an AE of treatment. Hence, the LUM/IVA NOAEL co-administration in 4 week duration rat study were 1000/50 mg/kg/day and the IVA/LUM/M28LUM NOAEL co-administration rat in 13 week duration study 25/500/10 mg/kg/day.

The changes in bodyweight/bodyweight gain, the hematologic and clinical chemistry observations caused by lumacaftor were generally transient and of small entity and are of doubtful or minimal toxicological importance. Changes in organ weights seem not to be an index of organ dysfunction: liver alterations are adaptive responses not considered toxicologically relevant and spleen increases are reasonably due to secondary haematological changes and to spontaneous chronic progressive neuropathy. In summary, liver, spleen and gastrointestinal system alterations are mainly due to spontaneous exacerbations in rodent following LUM/IVA co-adminsitration. Therefore, under experimental conditions, lumacaftor administered up to 13, 26 and 52 weeks in mice, rats and dogs, respectively, failed to identify target organ of toxicity, although definitive conclusion on this issue could be drawn only after the assessment of the ongoing two year rat carcinogenicity study. The NOAEL in mice, rats and dogs treated for 13, 26 and 52 week are 1000, 1000 and 500 mg/kg, respectively.

Overall, the combination of LUM/IVA did not affect the pharmacokinetics of each compounds; in rats and dogs, systemic exposures to lumacaftor and ivacaftor were generally similar to those seen after combination of each compound,exception given for IVA which showed accumulation. No new toxicities were revealed. In addition, the ivacaftor NOAEL in rats and dogs was reduced when combined with

lumacaftor as compared to ivacaftor alone, reflecting a greater sensitivity to ivacaftor in the presence of lumacaftor.

At the observed NOAEL, multiple exposures were reached for the majority of the studies, which would give a reasonable safety margin for most of the toxicity findings observed. Only for the M6IVA, the ivacaftor metabolite considered to be inactive, no safety margins were calculated in all studies. Toxicity of ivacaftor metabolites was individually not evaluated because the applicant considered M1-ivacaftor exposures at NOAEL in male rats to be high enough to provide adequate toxicology reassurance to extrapolate to human exposure.

Genotoxicity

Lumacaftor was non-genotoxic in a test battery comprehending the following assays: Ames test, CHO cells and in vivo micronucleous test. Since no toxico-kinetic investigation was included in the study, the evidence of exposure is claimed by the applicant because clinical signs of toxicity, characterised by piloerection in male mice at LUM 500, 1000 and 2000 mg/kg and lethargy in males at 2000 mg/kg, were observed in male mice. Ivacaftor was non-mutagenic and non-clastogenic in the ICH standard battery of genotoxicity tests. Since M1 and M6 are produced in vitro in animal liver preparations, it is highly likely that these ivacaftor metabolites are also non-mutagenic and non-clastogenic in vitro. Combination genotoxicity studies involving the co-administration of LUM and IVA were not performed and not considered necessary, since data available on each individual entity appear adequate for hazard identification and assessment of the genetic toxicity risk associated with co-administration.

Carcinogenicity

The lumacaftor lifetime (2-year) rat carcinogenicity study was ongoing at the time of this submission. The rat study design also includes an evaluation of a minor, yet disproportionate human metabolite of lumacaftor, M28-lumacaftor, which is formed at very low levels in mice and rats. The study design is claimed by the applicant agreed to by the Food and Drug Administration (FDA). Ivacaftor was not carcinogenic in mice and rats at the highest dosages tested (200 mg/kg/day in mice, corresponding to the AUC0-24h of 112 and 203 µg.h/mL in M and F respectively, and 50 mg/kg/day in rats, corresponding to the AUC0-24h of 467 and 853 µg.h/mL in M and F respectively). These exposures are in mice 5xM and 27xF the human exposure, and in rats 63xM and 116xF the human exposure. In addition, no pre-neoplastic lesions were seen in the mouse 3-month carcinogenicity dose range finding study, in the rat sub-chronic (3-month) and chronic (6-month) toxicity studies, or in the dog subchronic (3-month) and chronic (12-month) studies, suggesting a low potential for ivacaftor-induced tumour promotion. In the short term study (six month mice TgH2 carcinogenicity study), lumacaftor did not increase the incidence of neoplastic lesions. The tumor induced by LUM are among the most common spontaneous neoplasms in untreated Tg rasH2 mice (Morton et al., 2002), and not significant difference in the incidence between treated and controls are observed. Kidneys are the target organ for non-neoplastic lesions only in male mice, due to the presence of degenerative and regenerative changes. Since the M28LUM human circulating metabolites were not identified in Tg.rasH2 mice plasma, safety of the M28 human circulating metabolites of lumacaftor cannot appropriately assessed in this carcinogenicity studies, but this will be possible on the basis of findings of the ongoing two year rat carcinogenicity study, performed administering lumacafor and M28LUM metabolite .

Reproduction Toxicity

Lumacaftor/M28LUM does not affect male or female reproductive functions, as demonstrated in the rat fertility and early developmental study. Lumacaftor/M28-LUM did not cause reproductive system toxicity in male and female rats at 1000/20 mg/kg/day, respectively.

Ivacaftor did not cause reproductive system toxicity in male and female rats at 200 and 100 mg/kg/day, respectively. Dosages above of 100 mg/kg/day in females were associated to a 54% reduction in the

overall fertility index and number of pregnancies, significant reductions in the average number of corpora lutea and implantation sites with subsequent reductions in the average litter size and the average number of viable embryos per litter. Weight decreases of the seminal vesicles were observed in males treated at 200 mg/kg/day.

Lumacaftor was not teratogenic dosed orally to pregnant rats and rabbits during the organogenesis stage of foetal development at 2000 and 200 mg/kg/day (the highest dosage tested, corresponding to AUC 0-24h of 3320 µg.h/mL at GD 16 in rats and 1950 µg.h/mL at GD 19 in rabbits). The exposure at these doses is approximately 8x (rats) and 5x (rabbit) the mean systemic exposures of LUM in CF patients. In rabbits dosages > 50 mg/kg/day (AUC 995 µg.h/mL) produced maternal toxicity and abortion.

M28-LUM induced (see other studies section) foetal malformations and developmental variations only at extremely high maternal toxic doses, commonly inducing foetal alterations (800 mg/kg/day corresponding to AUC 0-24h of 4240 µg.h/mL at GD 16, approximately 120x the mean systemic exposures of M28-LUM in CF patients). On this basis M28-LUM is not consider teratogen.

Ivacaftor was not teratogenic administered orally to pregnant rats and rabbits during the organogenesis stage of foetal development at 100 and more than 100 mg/kg/day (the highest dosage tested), respectively. The exposure of both doses is approximately 45x the mean systemic exposures to ivacaftor in CF patients. In rats, dosages above 100 mg/kg/day produced reductions of foetal body weight and the the following skeletal development malformations: cervical ribs, incompletely ossified ribs, wavy ribs and sternal irregularities. These malformations are commonly observed at maternal toxic doses, so they were not considered teratogenic.

Lumacaftor/M28-LUM did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 1000/20 mg/kg/day. This corresponds to an exposure, in term of AUC 0-24h at DG 16, of about 2500 µg.h/mL, approximately 6x the mean systemic exposures of IVA in CF patients. F1 generation pups were indirectly exposed to LUM and M28-LUM through maternal transmission, during maternal gestation in utero and via maternal milk during the lactation period. Ivacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally from pregnancy through parturition and weaning at 100 mg/kg/day. Dosages higher than 100 mg/kg/day, were associated with reduction in survival and in lactation indices (92 and 98%, respectively) and in pup body weight.

Reproductive and developmental toxicity studies with LUM/IVA co-administration have not been performed since studies, conducted on each individual entity, were considered adequate to assess the risk associated with co-administration and provided no evidence for potential additive or synergistic interaction. Based on the available data, the overall reproductive and developmental risk associated with the combination regimen can be considered low. Juvenile animals studies are currently not required as the proposed LUM/IVA FDC indication target CF patients 12 years of age and older.

Toxicokinetic data

A comparison of steady-state exposures of lumacaftor/ivacaftor and their respective metabolites in nonclinical and clinical studies is provided in the table below. Human exposure is based on the proposed combination regimen of daily doses of 800 mg lumacaftor and 500 mg ivacaftor resulting in mean systemic exposures (AUC_{0-24h}) in CF patients of 396 and 7.32 µg·h/mL respectively. At these doses, AUC_{0-24h} of the lumacaftor metabolite, M28, is 33 µg·h/mL, and AUC_{0-24h} of the ivacaftor metabolites, M1 and M6 are 24.2 and 49.6 µg·h/mL respectively.

Comparison of lumacaftor and M28-lumcaftor exposure in non-clinical studies to clinical studies

Test Article	Study Type	Species	Period	Dose[a]	Analyte	Sex	AUC_{0-24h} (µg·hr/mL)	Ratio Animal AUC_{0-24h}/ Human AUC_{0-24h}
Lumacaftor	26-Week Carci.	Mouse	Day 178	2000	Lumacaftor	M	1390	3.5
				1500	Lumacaftor	F	2090	5.3
	6-Month Chronic	Rat	Day 180	1000/ 25[c]	Lumacaftor	M	1300	3.3
						F	3160	8.0
					M28	M	751	23
						F	1180	35
	EFD	Pregnant Rat	GD 17	2000	Lumacaftor	F	3320	8.4
		Pregnant Rabbit	GD 19	50	Lumacaftor	F	796	2.0
	12-Month Chronic	Dog	CM[b]	500	Lumacaftor	M	515	1.3
						F	429	1.1
M28	28-Day	Rat	Day 28	100	M28	M	1800	54
						F	2910	87
	EFD	Pregnant Rat	GD 17	400	M28	F	3360	101

The Applicant considered M28-lumacaftor a minor, human-specific metabolite, based on exposure in repeat dose clinical studies. M28-lumacaftor has been extensively characterised toxicologically, and can be therefore also considered to be adequately qualified as a major metabolite. M28-lumcaftor was not genotoxic, and did not result in target organ toxicity following repeat administration in rats. Fetal malformations were present in rats at doses where significant maternal toxicity was also present. M28-lumacaftor exposure at the NOAEL for developmental toxicity of 400 mg/kg was 101 fold higher than exposure at the maximum recommended human dose, indicating that this metabolite does not present a risk to humans. No separate toxicity studies with metabolites of ivacaftor were conducted as the exposure of M1-ivacaftor in rats was considered high enough at the NOAEL to provide adequate toxicology cover at human exposures at the intended therapeutic doses. Additional studies to characterize the toxicity of M1 and M6 were not feasible due to the difficulty in synthesizing sufficient quantities, combined with the fact that they have physicochemical and pharmacokinetic limitations to achieving higher exposures by direct IV or oral administration routes than those already achieved in the rat after oral ivacaftor administration. The exposure margin to the expected human therapeutic dose for M6-ivacaftor was less than 1 in all ivacaftor and lumacaftor/ivacaftor combination toxicity studies. It is acknowledged that practical issues limit the possibility for separate toxicity studies to characterise M6-ivacaftor. However, since concentrations of the M6 metabolite were also found to be higher in the lumacaftor/ivacaftor clinical studies compared with the monotherapy programme, it is considered that receptor binding and ion channel assays to assess the potential for off-target activity should be provided for this metabolite to provide reassurance. This wil be performed as a post authorisation study, as requested by the CHMP

Local Tolerance

The local tolerance of lumacaftor was assessed, to aid in setting worker protection levels, as exposure to the skin and eyes may occur during handling, particularly in the active substance manufacturing setting.Potential skin irritation of lumacaftor was assessed in an *in vitro* EPISKIN skin irritation test according to the OECD 439 guideline (protocol no VX-809-TX-020, final report not provided). Lumacaftor (10 ± 2 mg) was applied to human epidermis skin, EPISKIN, constructs consisting of human-derived epidermal keratinocytes, which had been cultured to form a multi-layered, highly differentiated epidermis

with a functional stratum corneum. Cell viability was determined after a 15 minute exposure period by reduction of 3-(4,5-dimethylthiazol-2-yl-2), 5,-diphenyltetrazolium bromide (MTT). Tissue viability following lumacaftor exposure was 99.2±4.9% compared to 100±4.9% in the negative control group, and lumacaftor was therefore predicted to be non-irritant to the skin. The potential for severe ocular corrosiveness and irritation of lumacaftor was assessed in the *in vitro* Bovine Corneal Opacity and Permeability (BCOP) assay, according to the OECD 437 guideline (protocol no VX-809-TX-021, final report not provided). Isolated bovine corneas were incubated with a 20% w/w lumacaftor suspension in 0.9% saline for 4 hours at 32ºC. Subsequently, corneal opacity was assessed using an opacitometer, and corneal permeability was measured by the leakage of sodium fluorescein from the anterior to the posterior of the cornea over a period of 90 minutes. By combining the results from these two endpoints, an *in vitro* irritancy score was deduced. This score was 6.0 for lumacaftor, and according to an established prediction model, lumacaftor was subsequently classified as a non-corrosive/non-severe eye irritant.

Ivacaftor was demonstrated to have no skin irritation potential following in vivo dermal exposure and to be noncorrosive/non-irritating to eye.

Overall, findings from available non-clinical studies suggest that lumacaftor and ivacaftor are non-irritant to both dermal and ocular surfaces and no irritation potential is expect from the combined use.

Other toxicity studies

While not discussed specifically in the dossier, lumacaftor is believed to have low potential for phototoxicity after oral administration. Presented UV absorption data show a peak at 293 nm. However, based on the absence of ophthalmology findings in repeat-dose studies, and the fact that no accumulation in the skin or eyes occurs after oral administration in distribution studies, the applicant considers the risk of phototoxicity negligible. The lack of a dedicated phototoxicity evaluation has been reflected in the SmPC, section 5.3.

Dependence studies have not been conducted for lumacaftor, since tissue distribution studies in rats have shown that lumacaftor does not cross the blood-brain-barrier to any appreciable extent. In addition, lumacaftor had no effects on central nervous system function in standard safety pharmacology studies in rats, in repeat-dose toxicity studies in mice, rats, and dogs, or on behaviour and learning in developing pups in the prenatal and postnatal development study.

All known and potential impurities including residual solvents in lumacaftor drug substance and drug product were either controlled to ICH classification limits or qualified in the repeat-dose animal toxicity studies described above, in additional genotoxicity assays conducted for specific substances with in silico predictions for mutagenicity (all 4 compounds tested which included starting materials and potential process impurities were negative), or based on published toxicity studies. Impurities VRT-087778 and VRT-0908591 were considered qualified based on the 3-month toxicity study conducted in dogs with lumacaftor. Specified impurities in the ivacaftor SDD drug product have been previously assessed and are adequately controlled.

2.3.5. Ecotoxicity / environmental risk assessment

Both lumacaftor and ivacaftor exceed the trigger value of >0.01 µg/L for the Phase I estimate of PECSURFACEWATER, and a Phase II environmental fate and effect analysis is therefore required for both substances. In addition, the octanol/water partition coefficients of ivacaftor and lumacaftor were close to the trigger value of 4.5, and fish bioaccumulation studies will be conducted as a part of the Phase II Tier B assessments.

For lumacaftor, studies on physical-chemical properties and fate and Phase II Tier A studies have been started, some are ongoing and some have been reported. The available data indicate that lumacaftor is

unlikely to represent a risk to groundwater and micro-organisms, and preliminary data indicate that lumacaftor is unlikely to reach the terrestrial compartment as a result of spreading of sewage sludge onto agricultural land. For ivacaftor, all studies are ongoing and no data are available.

Summary of main study results

Substance (INN/Invented Name): Lumacaftor					
CAS-number (if available): 936727-05-08					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD123	pH 4: 5.3 pH 7: 3.0 pH 9: 1.6			Potential PBT **No**
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	Close to trigger value at pH 7			not B (but fish bioaccumulation study required)
	BCF	Not required			not B
Persistence	DT50 or ready biodegradability	Not required			not P
Toxicity	NOEC or CMR	Not required			not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.026	µg/L			> 0.01 threshold **Yes**
Other concerns (e.g. chemical class)					**No**
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =			Study ongoing
Ready Biodegradability Test	OECD 301	Not conducted			Based on structure, not considered readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Study ongoing
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapita*	OECD 201	NOEC	304	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	9620	µg/L	Report not yet finalised
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC		µg/L	Study ongoing
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100,000	µg/L	
$PNEC_{water}$					Not determined
$PNEC_{microorganisms}$			962	µg/L	Assessment factor 10
$PNEC_{groundwater}$			10,000	µg/L	Assessment factor 10
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	Study not yet completed
Aerobic and anaerobic	OECD 307	DT50			Not required

transformation in soil		$\%CO_2$			
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	Not required
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	Not required
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	Not required
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	Not required
Sediment dwelling organism	OECD 218	NOEC		mg/kg	Study not yet completed

2.3.6. Discussion on non-clinical aspects

An appropriate non-clinical package has been submitted for lumacaftor and ivacaftor to support this MAA. Pharmacology, pharmacokinetics and toxicology of lumacaftor and ivacaftor, both separately and in combination, have been well-characterised. The rationale for developing the combination of lumacaftor and ivacaftor (Orkambi) for the treatment of cystic fibrosis patients homozygous for the F508del mutation has been supported by appropriate in vitro pharmacology studies in primary human bronchial epithelial cultures. Recent published evidence relating to the effect of ivacaftor on lumacaftor-corrected F508del-CFTR has been fully discussed by the applicant.

No target organ toxicity was identified in lumacaftor repeat dose toxicity studies in rats and dogs of up to 12 months duration and up to 3 months duration with the lumacaftor/ivacaftor combination. Ivacaftor has been confirmed to be non-carcinogenic. Lumacaftor was not genotoxic and not carcinogenic in the short-term alternative 26-week Tg.rasH2 transgenic carcinogenicity assay and the 2-year rat bioassay. Lumacaftor and ivacaftor are not teratogenic. Effects seen on fertility and early embryonic development, as well as pre-and postnatal development (ivacaftor only) have been adequately reflected in the SmPC.

Findings of cataracts were observed in juvenile rats dosed with ivacaftor at 0.32 times the maximum recommended human dose based on systemic exposure of ivacaftor and its metabolites when co-administered with lumacaftor as Orkambi. Cataracts were not observed in foetuses derived from rat dams treated during the organogenesis stage of foetal development, in rat pups exposed to a certain extent through milk ingestion prior to weaning, or in repeated dose toxicity studies with ivacaftor. The potential relevance of these findings in humans is unknown. This is included in the SmPC.

Since concentrations of the M6 metabolite were also found to be higher in the lumacaftor/ivacaftor clinical studies compared with the monotherapy programme receptor binding and ion channel assays to assess the potential for off-target activity should be provided for this metabolite in post-authorisation phase as described in the RMP. Furthermore, the applicant agreed to investigate the potential inhibition of OAT1, OAT3, OCT1 and OCT2 by ivacaftor and lumacaftor as described in the RMP.

The current available data on the ERA programme do not allow a definitive conclusion on the potential risk of lumacaftor and ivacaftor to the environment, and the applicant agreed to perform the required studies and complete the lumacaftor and ivacaftor ERAs post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the CHMP was of the opinion that the non-clinical profile of Orkambi was adequately characterised. Results from pharmacokinetics studies, the choice of species as well as the outcome of the toxicology studies are in full support of granting the MAA for Orkambi.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the

CHMP recommends the following points be addressed: Submission of further ERA studies is expected by the end of 2015.

2.4. Clinical aspects

This application for Orkambi is supported by 17 clinical studies, which evaluated lumacaftor monotherapy or a combination of lumacaftor/ivacaftor therapy. Of these studies, 15 were completed and 2 were ongoing at the time of filing. The clinical development programme includes 12 phase I studies in healthy volunteers/subjects without cystic fibrosis and 5 phase II/III studies in CF patients. In addition there are studies with ivacaftor monotherapy which have already been considered during the assessment of the MAA of Kalydeco. These include VX06-770-003, which is the PK study using radiolabelled ivacaftor, VX08-770-104 which evaluated the effects of ivacaftor in CF patients homozygous with F508del-CFTRs and VX08-770-105 which is the long-term extension of VX08-770-104.

The ongoing studies include a PK study (011) in 6-11 years, which is a development to support a future extension of the indication to children aged between 6-11 and a long-term uncontrolled study (study 105) to provide evidence on long-term safety and maintenance of efficacy.

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Identifier (Abbreviation)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) (Formulation); Dosage Regimen; Route of Administration	Number of Subjects Dosed/ Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Patient PD and PK/PD Studies						
Phase 2a PK, PD	VX08-809-101	Primary Objective Evaluate safety and tolerability of LUM in subjects with CF who are homozygous for the *F508del-CFTR* mutation Secondary Objectives ☐ Evaluate effect of LUM on biomarkers of CFTR activity, pulmonary function, and patient-reported outcomes in subjects with CF who are homozygous for the *F508del-CFTR* mutation ☐ Evaluate PK of LUM in subjects with CF who are homozygous for the *F508del-CFTR* mutation ☐ Determine a dose of LUM for further clinical study	Randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, dose-finding, multicenter	**LUM:** 25-mg and 50-mg capsules **Placebo:** LUM-matching capsules **Cohort 1 (Group A)** LUM 25 mg or 50 mg qd or placebo **Cohort 2 (Group B)** LUM 100 mg or 200 mg qd or placebo oral administration	89 subjects Male and female subjects with CF who are homozygous for the *F508del-CFTR* mutation aged 18 years or older	LUM monotherapy for 28 days
Phase 2 PK, PD	VX09-809-102	**Cohort 1 (Homozygous)** Primary Objectives ☐ Evaluate safety and tolerability when LUM is administered alone or in combination with IVA ☐ Evaluate effect of LUM administered alone or in combination with IVA on sweat chloride Secondary Objectives ☐ Evaluate effect of LUM administered alone or in combination with IVA on pulmonary function ☐ Evaluate effect of LUM administered alone on sweat chloride ☐ Assess PK of LUM and M28-LUM when LUM is administered alone and in combination with IVA (including M1-IVA and M6-IVA)	Double-blind, placebo-controlled, multiple-dose, dose-finding	**LUM (Form 1):** 200-mg tablet **IVA (film-coated):** 100-mg and 150-mg tablets **LUM/IVA (fixed-dose, film-coated):** 200-mg LUM/125-mg IVA tablet **Placebo:** LUM-matching, IVA-matching, fixed dose LUM/IVA-matching tablets **Cohort 1** Group 1 (Homozygous): LUM 200 mg qd followed by LUM 200 mg qd/IVA 150 mg q12h	312 subjects **Cohort 1:** 62 subjects **Cohort 2:** 109 subjects **Cohort 3:** 15 subjects **Cohort 4:** 125 subjects **Cohort 1 and Cohort 3** Male and female subjects with CF who are homozygous for the *F508del-CFTR*	**Cohort 1** 14 days of LUM monotherapy or placebo followed by 7 days of LUM/IVA combination therapy or placebo **Cohort 2 and Cohort 3** 28 days of LUM monotherapy or placebo followed by 28 days of LUM/IVA

					mutation aged 18 years or older	combination
Type of Study	**Study Identifier (Abbreviation)**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) (Formulation); Dosage Regimen; Route of Administration**	**Number of Subjects Dosed / Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
		Cohort 2 (<u>Homozygous or Heterozygous</u>) <u>Primary Objectives</u> ☐ Evaluate safety and tolerability when LUM is administered alone or in combination with IVA ☐ Evaluate effect of LUM is administered alone or in combination with IVA on sweat chloride <u>Secondary Objectives</u> ☐ Evaluate effect of LUM is administered alone or in combination with IVA on pulmonary function ☐ Evaluate effect of increasing doses of LUM administered alone on sweat chloride ☐ Evaluate effect of LUM is administered alone or in combination with IVA on CFQ-R score ☐ Assess PK of LUM and M28-LUM when LUM is administered alone or in combination with IVA (including M1-IVA and M6-IVA) **Cohort 3 (<u>Homozygous</u>)** <u>Primary Objectives</u> ☐ Evaluate safety and tolerability when LUM is administered alone or in combination with IVA ☐ Evaluate efficacy of LUM is administered alone or in combination with IVA on sweat chloride		<u>Group 2 (Homozygous):</u> LUM 200 mg qd followed LUM 200 mg qd/IVA 250 mg q12h <u>Group 3 (Homozygous):</u> placebo **Cohort 2** <u>Group 1(Homozygous):</u> LUM 200 mg qd followed LUM 200 mg qd/IVA 250 mg q12h <u>Group 2 (Homozygous):</u> LUM 400 mg qd followed by LUM 400 mg/IVA 250 mg q12h <u>Group 3 (Homozygous):</u> LUM 600 mg qd of followed by LUM 600 mg qd/IVA 250 mg q12h <u>Group 4 (Heterozygous):</u> LUM 600 mg qd followed by LUM 600 mg qd/IVA 250 mg q12h <u>Group 5 (Homozygous or Heterozygous):</u> placebo **Cohort 3** <u>Group 1 (Homozygous):</u> LUM 400 mg q12h followed by LUM 400 mg q12h/IVA 250 mg q12h	**Cohort 2** Male and female subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation aged 18 years or older **Cohort 4** Male and female subjects with CF who are heterozygous for the *F508del-CFTR* mutation aged 18 years or older	therapy or placebo **Cohort 4** 56 days of LUM/IVA combination therapy or placebo

				Group 2 (Homozygous): placebo		

Type of Study	Study Identifier (Abbreviation)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) (Formulation); Dosage Regimen; Route of Administration	Number of Subjects Dosed / Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		Secondary Objectives ☐ Evaluate effect LUM is administered alone or in combination with IVA on pulmonary function ☐ Evaluate effect of increasing doses of LUM administered alone on sweat chloride ☐ Evaluate effect of LUM is administered alone or in combination with IVA on CFQ-R score ☐ Assess PK of LUM and M28-LUM when LUM is administered alone or in combination with IVA (including M1-IVA and M6-IVA) **Cohort 4 (Heterozygous)** Primary Objectives ☐ Evaluate safety and tolerability of LUM in combination with IVA ☐ Evaluate efficacy of LUM in combination with IVA Secondary Objective Assess PK of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA		**Cohort 4** Group 1 (Heterozygous): LUM 400 mg q12h/IVA 250 mg q12h Group 2 (Heterozygous): placebo oral administration		

Type of Study	Study Identifier (Abbreviation)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) (Formulation); Dosage Regimen; Route of Administration	Number of Subjects Dosed / Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety Studies						

Controlled Clinical Studies Pertinent to the Claimed Indication						
Phase 3 Efficacy and safety	VX12-809-103	Primary Objective Evaluate efficacy of LUM in combination with IVA at Week 24 in subjects with CF who are homozygous for the *F508del-CFTR* mutation Secondary Objectives ☐ Evaluate safety LUM in combination with IVA through Week 24 ☐ Investigate PK of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	**LUM/IVA (fixed-dose, film-coated):** 200-mg LUM/125-mg IVA tablet and 200-mg LUM/83-mg IVA tablet **IVA (film-coated):** 125-mg tablet **Placebo (film-coated):** fixed-dose LUM/IVA matching tablet or IVA-matching tablet ☐ LUM 600 mg qd/IVA 250 mg q12h ☐ LUM 400 mg q12h/IVA 250 mg q12h ☐ LUM placebo q12h/IVA placebo q12h oral administration	549 subjects Male and female subjects with CF who are homozygous for the *F508del-CFTR* mutation aged 12 years or older	Up to 24 weeks + 5 days
Type of Study	**Study Identifier (Abbreviation)**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) (Formulation); Dosage Regimen; Route of Administration**	**Number of Subjects Dosed/ Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Phase 3 Efficacy and safety	VX12-809-104	Primary Objective Evaluate efficacy of LUM in combination with IVA at Week 24 in subjects with CF who are homozygous for the *F508del-CFTR* mutation Secondary Objectives ☐ Evaluate safety LUM in combination with IVA through Week 24 ☐ Investigate PK of LUM, M28-LUM, IVA, M1-IVA, and M6-IVA	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	**LUM/IVA (fixed-dose, film-coated):** 200-mg LUM/125-mg IVA tablet and 200-mg LUM/83-mg IVA tablet **IVA (film-coated):** 125-mg tablet **Placebo (film-coated):** fixed-dose LUM/IVA matching tablet or IVA-matching tablet ☐ LUM 600 mg qd/IVA 250 mg q12h	559 subjects Male and female subjects aged 12 years or older with CF who are homozygous for the *F508del-CFTR* mutation	Up to 24 weeks + 5 days

				☐ LUM 400 mg q12h/IVA 250 mg q12h ☐ LUM placebo q12h/IVA placebo q12h oral administration		
Type of Study	**Study Identifier (Abbreviation)**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product(s) (Formulation); Dosage Regimen; Route of Administration**	**Number of Subjects Dosed/ Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**
Uncontrolled Clinical Studies						
Phase 3 Safety and efficacy	VX12-809-105	Primary Objective **Part A and Part B** Evaluate long-term safety and tolerability of LUM in combination with IVA in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation, who are in the Part A and Part B Treatment Cohorts Secondary Objectives **Part A** ☐ Evaluate long-term efficacy and durability of LUM in combination with IVA for subjects in the Part A Treatment Cohort ☐ Evaluate post-treatment safety and tolerability of LUM in combination with IVA for subjects in the Part A Observational Cohort **Part B** Evaluate long-term efficacy and durability of LUM in combination with IVA for subjects in the Part B Treatment Cohort	Parallel-group, multicenter, rollover	**LUM/IVA (fixed-dose, film-coated):** 200-mg LUM/125-mg IVA tablet and 200-mg LUM/83-mg IVA tablet **IVA (film-coated):** 125-mg tablet **Part A (Treatment Cohort only):** ☐ LUM 600 mg qd/IVA 250 mg q12h ☐ LUM 400 mg q12h/IVA 250 mg q12h **Part B:** LUM 400 mg q12h/IVA 250 mg q12h oral administration	1165 subjects planned (1050 subjects from Studies 103 and 104 and 115 subjects from Study 102 Cohort 4) *at time of report: 1031 subjects in Part A Treatment Cohort; 19 subjects in Part A Observational Cohort; 115 subjects in Part B* **Part A:** Male and female subjects aged 12 years or older with CF who are homozygous for the *F508del-CFTR* mutation **Part B:** Male and female subjects aged 12 years or older with CF who are heterozygous for the *F508del-CFTR* mutation	Approximately 96 weeks

2.4.2. Pharmacokinetics

The pharmacokinetics of ivacaftor was adequately characterised and has been assessed in the MAA of ivacaftor (Kalydeco). To support this application, the applicant has characterised the PK of lumacaftor monotherapy and the PK of both ivacaftor and lumacaftor, when they are co-administered and when they are administered together as a fixed-dose combination tablet. In line with the legal basis of this application, the data on ivacaftor (previously authorised as Kalydeco) were adequately assessed for the purpose of this application for the FDC. The new data submitted in support of this application includes 11 phase I clinical studies in healthy volunteers, one phase I study in patients with moderate hepatic injury and PK data from five phase II/III studies in cystic fibrosis patients.

Analytical methods

Lumacaftor

An analytical method was established and validated for the determination of lumacaftor and M28-Lumacaftor in human plasma with K2 EDTA or K3 by HPLC with MS/MS detection. The lower limit of quantification (LLOQ) and upper limit of quantitation (ULOQ) were 2.00 ng/mL and 2000 ng/mL, respectively for lumacaftor. The method met the requirements for selectivity, sensitivity, precision, and accuracy, and showed no carryover from analyte or internal standard. Throughout the lifecycle of the method, there were some small changes to the method, typically associated with assay improvements or method transfers to a contract research organization (CRO).

Ivacaftor

Ivacaftor was quantitated in plasma in all combination studies, using a validated analytical method. Ivacaftor's major metabolites, M1- and M6-ivacaftor, were also quantitated in plasma in all combination studies (except in Study 007), using a validated analytical method. The assay method was sufficiently selective for endogenous substances and met the requirements for precision and accuracy at each level for ivacaftor, M1-ivacaftor, and M6-ivacaftor.

Absorption

Lumacaftor has low aqueous solubility and high permeability assessed via the colorectal adenocarcinoma (Caco-2) cell system. Although pH-dependent solubility was observed, the lumacaftor drug substance is practically insoluble in water and buffer solutions of pH 1.0 to pH 8.0. Therefore, lumacaftor is suggested to be a BCS Class 2 (low solubility/high permeability) compound. Ivacaftor could not be classified definitively by the BCS. It has low solubility, suggesting that it is either a BCS Class 2 (low solubility/ high permeability) or Class 4 (low solubility/low permeability) drug. However, its low solubility and non-specific binding to culture materials precluded an acceptable determination of its permeability using the Caco-2 cell system. Following multiple oral dose administrations of lumacaftor, the exposure of lumacaftor increased roughly proportionally with dose from 50 to 1000 mg qd. In subjects with CF, the lumacaftor Cmax and AUC also increases approximately proportional with the dose over the LUM 25 mg qd to 400 mg q12h dose range. The exposure of lumacaftor increased approximately 1.6- to 2.0-fold when given with fat containing food (Study 012). The median (range) time of the maximum concentration (tmax) is approximately 4.0 (2.0, 9.0) hours in the fed state. Following multiple oral dose administration of ivacaftor in combination with lumacaftor, the exposure of ivacaftor generally increased with dose from 150 mg q12h to 250 mg q12h (Study 006). The exposure of ivacaftor when given in combination with lumacaftor increased approximately 2.5- to 3.4-fold when given with food containing fat (Study 012). Therefore, ivacaftor given in combination with lumacaftor should be administered with fat-containing food. The median (range) tmax is approximately 4.0 (2.0, 6.0) hours in the fed state.

Bioavailability

No intravenous data is available therefore relative bioavailability cannot be determined. Both compounds show reasonable systemic bioavailability following oral dosing in man. The Tmax for lumacaftor is 3- 6 hours and Cmax following the proposed dose of 400 mg bid is 23.7 µg/ml. The tmax for ivacaftor when administered in the fixed dose combination is approximately 4 hours and Cmax for the proposed dose of 250mg bid is 1.33 µg/ml.

Bioequivalence

Various formulations have been used in the development of lumacaftor and in combination which includes suspension, capsules and tablets. Comparative exposure of the different formulations of lumacaftor was seen in single dose studies in healthy volunteers. Exposure of the suspension is lower than that seen for capsules and tablets. Early clinical studies were conducted with the co-administration of both ivacaftor and lumacaftor. A cross-over study (007) was conducted to evaluate the relative bioavailability of the fixed dose combination tablet as compared to the separate tablets. The tablet and FDC appear to be bioequivalent, and the only parameter that did not meet standard bioequivalence criteria is the Cmax of ivacaftor (GLSMR [90% CI] - 1.20 [1.09, 1.33]). However for practical purposes this is acceptable and the PK results from tablet formulation can be considered applicable to the FDC as well.

Influence of food

Bioavailability of ivacaftor tablet formulations increases approximately 2.5- to 4-fold when administered with food and ivacaftor is therefore recommended to be administered with fat-containing food, as reflected in the SmPC. The effect of food on the relative bioavailibity of lumacaftor and ivacaftor when administered as a fixed dose combination was evaluated in study 012. This study showed that exposure of both lumacaftor and ivacaftor was increased when administered with a high-fat meal.

Distribution

Lumacaftor and ivacaftor are extensively bound to plasma proteins (approximately 99%), with lumacaftor binding to albumin and ivacaftor to alpha-1-glycoprotein & albumin. Distribution parameters of lumacaftor were estimated in single- and multiple-dose studies in healthy subjects and via a population PK modeling approach. In the single- and multiple-dose escalation study (Study 001), lumacaftor had a moderate mean apparent volume of distribution (~36 to 53 L) over the 25- to 400-mg dose range studied. From the population PK analysis, the typical estimates of final PK model parameters (%CV) for the reference covariate effects (70 kg, 18 years, and CF subject) were 2.38 L/h (29.4%) for CL/F and, 23.5 L (48.7%) for Vc/F, 33.3 L (30.5%) for Vp/F, and 3.65 L/h (35.2%) for Q/F. Ivacaftor has a large apparent volume of distribution, suggesting penetration of ivacaftor into tissues. From the population PK analysis, the typical estimates of final PK model parameters (%CV) for the reference covariate effects (70 kg, 18 years, and CF subject) were 25.1 L/h (40.5%) for CL/F, 95.0 L (53.9%) for Vc/F, 201 L (26.6%) for Vp/F, and 23.9 L/h for Q/F.

Metabolism

Lumacaftor is not extensively metabolized in human with the majority of lumacaftor excreted unchanged in the faeces. In vitro and in vivo data indicate that lumacaftor is mainly metabolised via oxidation and glucuronidation. The transporter responsible for the biliary excretion has not been identified. Hydroxy-lumacaftor (M1-lumacaftor; later referred to as M22-lumacaftor) was the primary metabolite observed following incubation of lumacaftor with liver microsomal preparations, while lumacaftor glucuronide (M2-lumacaftor) was the primary metabolite detected following incubation of lumacaftor with hepatocytes. M1-lumacaftor and M2-lumacaftor were also observed to be the circulating metabolites of lumacaftor in rats and dogs; however, these metabolites were not considered to be major metabolites as their levels were less than 10%. Following administration of a single oral dose of [14C]-LUM 200 mg (100

uCi), most of the circulating radioactivity in plasma was associated with the parent drug and M28-lumacaftor. M28 lumacaftor has a long terminal half-life (approximately 100 hours). Approximately 62% of the radioactivity was associated with unchanged lumacaftor. M28-lumacaftor represented 21% of the total radioactivity and a metabolite:parent AUC ratio of 35%. No other metabolite exposure exceeded a 5.4% metabolite ratio. These findings indicated that the majority of exposure in plasma was related to the unchanged lumacaftor. Similar to plasma, unchanged [14C]-lumacaftor was the major component excreted in faeces. The renal route of elimination of [14C]-lumacaftor is negligible.

Ivacaftor is extensively metabolized in humans. In vitro and in vivo data indicate that ivacaftor is primarily metabolized by CYP3A. M1-ivacaftor and M6-ivacaftor are the 2 major metabolites of ivacaftor in humans. M1-ivacaftor has approximately 1/6th the potency of ivacaftor and is considered pharmacologically active. M6-ivacaftor has less than 1/50th the potency of ivacaftor and is not considered pharmacologically active. After 150 mg q12h of the commercial tablet formulation in the fed state, the mean AUC ratio was approximately 2.7 for M1/ivacaftor and approximately 2.8 for M6/ivacaftor. As ivacaftor is metabolised by CYP3A and lumacaftor induces CYP3A, this will increase the contribution of CYP 3A4 to the elimination. The potential for inducing metabolism of ivacaftor when administered as FDC was studied in Study 005, which 005 showed that mean VX-809 plasma concentration time profiles were similar after the administration of VX-809 alone or in combination with VX-770. M28 metabolite showed slightly higher concentrations on Day 1 and Day 14 of the combination treatment period relative to the VX-809 alone treatment period.

Plasma concentration-time profiles of VX-770 and M1 were comparable after the administration of VX-770 alone or in combination with VX-809 after a single dose. However after multiple dosing for 14 days, there was a massive reduction in VX-770 and M1 plasma concentrations when VX-770 was co-administered with VX-809 as summarized below.

Effect of VX-809 on VX-770 PK:GLSM Ratio (With/Without VX-809) and Confidence Intervals

Analyte	Parameter	N	Day	GLSM Ratio (%)	90% CI Lower (%)	90% CI Upper (%)
VX-770	C_{max}	17	1	91.84	81.56	103.4
		17	14	24.10	18.58	31.27
	AUC_{0-12}	17	1	98.19	88.16	109.4
		17	14	19.50	15.07	25.22
M1	C_{max}	17	1	80.22	71.54	89.95
		17	14	37.46	31.22	44.94
	AUC_{0-12}	17	1	85.77	77.67	94.72
		17	14	28.25	23.78	33.55
M6	C_{max}	17	1	104.2	92.96	116.9
		17	14	96.57	82.74	112.7
	AUC_{0-12}	17	1	106.1	94.40	119.2
		17	14	89.46	77.97	102.6

AUC_{0-12}=The area under the plasma concentration-time curve from time 0 to time 12 hours
CI=Confidence interval
C_{max}=Maximum observed plasma concentrations
Day=Day relative to the initial dose of study drug within a treatment period
GLSM=Geometric Least Squares Mean
GLSM Ratio=(VX-770 GLSM with VX-809/VX-770 GLSM without VX-809)

The above results necessitate the use of the higher dose of ivacaftor (250mg bd) when administered as combination with lumacaftor as compared to the licensed ivacaftor monotherapy dose (150mg bd).

However, even with the increased dose, concentrations of Ivacaftor and M1 are markedly lower than those seen with monotherapy (table below).

Ta Summary of Clinical Exposures (AUC) of IVA, M1-IVA, and M6-IVA Between the IVA Monotherapy and LUM/IVA Combination Programs

Analyte	IVA Monotherapy	LUM/IVA[c] Without Itraconazole	LUM/IVA[c] With Itraconazole
Ivacaftor	11800 to17400[a]	2310	10000
M1-ivacaftor	20800 to 23100[b]	8870	21200
M6-ivacaftor	20100 to 23800[b]	29900	29400

Sources: data on file
AUC: area under the concentration versus time curve; DDI: drug-drug interaction; IVA: ivacaftor; LUM: lumacaftor.
[a] Range of mean AUC values observed in ivacaftor monotherapy Phase 3 Studies (VX08-770-102 and VX08-770-103).
[b] Range of mean AUC values observed in Studies VX12-770-016 and VX13-770-017.
[c] Mean AUC values from Study VX12-809-009 DDI study with itraconazole.

Elimination

Elimination in the faeces was the predominant route of elimination for lumacaftor and its metabolites in human ADME Study 004, with minimal renal excretion. Following administration of a single oral dose of [14C]-LUM 200 mg in healthy male subjects, the mean recovery of total radioactivity in urine and faeces samples ranged from 94% to 100% (mean of 98%). Individual faecal recoveries ranged from 81% to 93% of the administered dose (mean of 90%), and individual urinary recoveries ranged from 6.9% to 13% (mean of 8.6%). Most of the radioactivity observed in faeces was associated with unchanged lumacaftor and a monohydroxylated metabolite (M22-lumacaftor), accounting for an average of 51% (lumacaftor) and 17% (M22-lumacaftor) of the radioactive dose in Study 004. These findings as well as the low levels of plasma-circulating glucuronides indicate that the majority of lumacaftor was likely eliminated unchanged from the body into the faeces.

Dose proportionality and time dependencies

Steady-state plasma concentrations of lumacaftor in healthy subjects were generally reached after approximately 5 to 14 days of treatment. Based on AUC, the accumulation ratio in plasma on Day 14 following LUM qd dosing ranged from 1.9 to 2.2 across the tested dose levels (LUM 50 to 200 mg). The PK profile of lumacaftor was investigated in subjects with CF following multiple oral dosing. The t1/2 and accumulation findings are consistent with the data observed in healthy subjects, the median steady-state AUCs in subjects with CF were approximately 2-fold lower than that of Study 005 in healthy subjects when comparing the same dose (200 mg qd). A similar effect was seen on the M28 metabolite. The metabolite to parent drug ratio (M28-lumacaftor/lumacaftor) based on AUC at steady state decreased from 33% at a LUM 25 mg/day dose to 8% at a LUM 800 mg/day dose after 28 days of lumacaftor treatment.

Ivacaftor shows a decrease in exposure on multiple dosing due to induction by lumacaftor and a higher dose of 250 mg is proposed. It is proposed that the exposure with this higher dose is still lower than that seen for 150 mg monotherapy.

Population PK

Population PK analyses for repeated-measures endpoints were conducted via nonlinear mixed effects modeling with a qualified installation of the nonlinear mixed effects modeling (NONMEM) software. The population PK showed that lumacaftor CL/F decreased with increasing age, with a point estimate of -0.265 for the effect estimate. For the typical 12 year old, this translates to an 11% greater CL/F when compared to the reference 18 year old. For the typical 50 year old subject, this translates to a CL/F value that is 24% lower than the reference 18 year old. Lumacaftor bioavailability was 1.81 times higher in healthy subjects

and D1 was increased by a factor of 1.34, while ka and ALAG were decreased by factors of 0.663 and 0.514, respectively. The higher exposre in healthy subjects is attributed to an effect on absorption however the mechanism and implications of this have not been discussed. Body weight was an important predictor of variability in ivacaftor CL=F. Ivacaftor CL=F was 39% and 131% of the reference value of 25.1 L/h for the typical 20 kg and 100 kg subject, respectively, when compared to the reference subject (70 kg).

Ivacaftor bioavailability was 1.53 times higher in healthy subjects. The reason for this is not known; since prior analyses have indicated that bioavailability in CF subjects is equivalent when comparing healthy subjects to CF subjects. Studies 011 and 102 are the only two studies contributing ivacaftor data. Since the study population of 011 was small, it is likely that Study 102 is affecting the overall estimate. It is possible that the bioavailability difference can be attributed to inter-study variability.

The population PK modelling is comprehensive and appears to have been well performed. The demographics of the data set is limited with limited representation of race other than white and the oldest individual being only 57 years old and the heaviest being 107 kg. This is understandable in the context of the demographics of the target patient population. The approach taken in the analysis of covariates is atypical with it being based on emphasising parameter estimation rather than stepwise hypothesis testing. The support for this approach given by the company seems reasonable and this was based on data from the phase I/II studies, thus shrinkage should not be an issue. It would have been useful to have seen OFVs for the models, however it is noted that there is a small improvement in residual variability following inclusion of the covariates. The modelling is used to investigate covariates and for PKPD modelling of the phase III data, however this data is only used as supportive data. VPC's are provided stratified by study and dose and boot strapping of final parameter estimates. There are no individual plots of observed versus predicted concentrations which would be expected, however given the detailed VPCs this can be accepted. Weight is fixed with the expected exponents of 0.75 and 1.0 for clearance and volume of distribution respectively. It would normally be expected that these exponents would be determined by the model however plots are supportive of this relationship for adults. It is questioned whether weight and age are both needed in the model considering that the age range is 6 years and above and given the limited demographics. It is considered that the modelling is acceptable to support dosing in patients over the included demographic range.

Special populations

The PK of lumacaftor and ivacaftor has not been studied in subjects with renal impairment as the initial PK data suggests that there was minimal excretion of the parent drug and metabolites in the urine. A study in renal impairment is normally required even for drugs that are not renally cleared due to the effect of uremic factors on hepatic clearance. An analysis on CRCL was performed in the POPPK analysis and no effect of mild or moderate impairment was seen on the PK. Study 010 was conducted to evaluate PK after lumacaftor and ivacaftor combination therapy in subjects with moderate hepatic impairment, according to Child-Pugh B classification. The impact of mild hepatic impairment (Child-Pugh A) on the PK of lumacaftor given in combination with ivacaftor has not been studied, but the increase in exposure is expected to be less than 50%. Therefore, no dose adjustment is necessary for patients with mild hepatic impairment. Following multiple doses of lumacaftor in combination with ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh B) had higher exposures (AUC_T by approximately 50% and Cmax by approximately 30%) compared with healthy subjects matched for demographics. Therefore, the dose should be reduced by 25% for patients with moderate hepatic impairment. Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh C); however, exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, after weighing the risks and benefits of treatment, Orkambi should be used with caution at a maximum dose of lumacaftor 400 mg/ivacaftor 250 mg total daily dose, given as one tablet in the morning and one tablet in the evening. The SmPC includes the adequate guidance on treatment of patients with hepatic disorders.

Pharmacokinetic interaction studies

Based on studies in cultured human hepatocytes, lumacaftor has the potential to induce CYP3A4, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. Lumacaftor was a moderate inhibitor of CYP2C8 in vitro. Ivacaftor has potential to inhibit CYP2C8 and CYP2C9 in vitro. As per the SmPC recommendations, no dose adjustment is necessary when CYP3A inhibitors are initiated in patients currently taking Orkambi. When initiating Orkambi in patients taking strong CYP3A inhibitors, the dose should be reduced to one tablet daily (lumacaftor 200 mg/ivacaftor 125 mg total daily dose) for the first week of treatment to allow for the steady state induction effect of lumacaftor. Following this period, the recommended daily dose should be continued.

There was no meaningful impact of ivacaftor on the PK of both lumacaftor and M28-lumacaftor when the 2 study drugs were co-administered at a dose of LUM 200 mg q24h/IVA 150 mg q12h for 14 days, although the exposures of lumacaftor was relatively lower in the presence of ivacaftor. There was however a large decrease in plasma exposure of ivacaftor (~ 80%), but no meaningful impact on the exposure of M6-ivacaftor when the 2 study drugs were co-administered at a dose of LUM 200 mg q24h/IVA 150 mg q12h for 14 days. These results are consistent with the predicted induction of CYP3A by lumacaftor. Lumacaftor decreases the exposure of ivacaftor due to induction of P450. Ivacaftor appears to cause a small decrease in the exposure of lumacaftor however this is attributed to clinical variability.

Study 009 also evaluated the effect of long- and short-acting bronchodilators in healthy adult subjects treated with lumacaftor in combination with ivacaftor. The PK of lumacaftor and ivacaftor were comparable on co-administration with the various bronchodilators used in the study. A prototypical probe study for the effect of lumacaftor on a CYP3A substrate such as midazolam was not conducted due to the fact that ivacaftor is a sensitive CYP3A substrate, which showed the expected large effect with substantial reductions in exposure due to lumacaftor induction. Itraconazole had no effect on the PK of lumacaftor and M28-lumacaftor, but caused a substantial increase (by 4.3-fold) in the exposure of ivacaftor when given in combination with lumacaftor. A lower magnitude of increase (2.4-fold) was observed in the exposures of M1-ivacaftor in the presence of itraconazole; however, there was no change in the exposure of M6-ivacaftor. Although itraconazole caused a substantial increase in the exposure of ivacaftor when given in combination with lumacaftor, due to the induction of CYP3A by lumacaftor, the net ivacaftor exposure does not exceed that when given in the absence of lumacaftor at a dose of 150 mg q12h (the approved dose for ivacaftor monotherapy). Therefore, no change in the dose of lumacaftor and ivacaftor combination therapy is recommended for co-administration with strong CYP3A inhibitors.

Ciprofloxacin had minimal effect on the PK of lumacaftor and M28-lumacaftor, but caused a mild increase in the exposure of ivacaftor when given in combination with lumacaftor. The increase in exposure of ivacaftor is not considered significant as the exposures were substantially lower than ivacaftor monotherapy (150 mg q12h) exposures. The results indicate ciprofloxacin has a minimal to mild effect on lumacaftor and ivacaftor exposure; therefore no change in the dose of lumacaftor and ivacaftor combination therapy is recommended when co-administered with ciprofloxacin. Rifampin altered the shape of the concentration time profile of lumacaftor but had no substantial impact on the overall exposure. M28-lumacaftor exposures mildly increased (~35%) in the presence of rifampin. Rifampin induces the metabolism of CYP3A, the enzyme primarily responsible for the metabolism of ivacaftor. When given in combination with rifampin, the exposures of ivacaftor substantially decreased (~50%), M1-ivacaftor exposure mildly decreased (~35%), and M6-ivacaftor mildly increased (~29%). Based on these results, co-administration of lumacaftor and ivacaftor combination therapy with rifampin or any strong inducer of CYP3A is not recommended because ivacaftor exposure will be decreased, which may lead to loss of efficacy.

The effects of lumacaftor monotherapy or lumacaftor in combination with ivacaftor on the PK of hormonal contraceptives are not known; however, since lumacaftor is an inducer of CYP3A, it may reduce the

effectiveness of hormonal contraceptives. Hormonal contraceptives should not be relied on as an effective method of contraception when co-administered with lumacaftor and ivacaftor combination therapy. The SmPC for Orkambi fully describes the potential interactions of ivacaftor and/or lumacaftor with other medicinal products.

2.4.3. Pharmacodynamics

The PD of lumacaftor have been assessed in studies evaluating lumacaftor monotherapy (Studies 101 and 102) and/or lumacaftor and ivacaftor combination therapy (Study 102) in subjects with CF who are homozygous (Studies 101 and 102) or heterozygous (Study 102) for the F508del-CFTR mutation. Results from Study 102 demonstrated proof of concept that pharmacologic modulation of CFTR function through treatment with lumacaftor in combination with ivacaftor can result in clinical benefit in subjects who are homozygous for the F508del-CFTR mutation. A phase 3 study, study 770-104 which evaluated ivacaftor monotherapy in cystic fibrosis patients who were homozygous with F508del-CFTR was assessed as part of the ivacaftor MAA. This study provides important evidence in the context of this application for the lack of efficacy of ivacaftor monotherapy in this patient population.

Mechanism of action

Ivacaftor is a potentiator of the CF transmembrane conductance regulator (CFTR) that increases the channel activity of CFTR protein located at the cell surface through increased gating activity, resulting in increased chloride transport. For ivacaftor to act, the CFTR channel must first be activated by cAMP-dependent protein kinase A (PKA). That would exclude on theoretical grounds that ivacaftor has any effect in class I and II mutations. Ivacaftor potentiated chloride transport of G551D-CFTR protein, in both recombinant cells carrying the G551D-CFTR mutation and primary cultures of HBE isolated from the bronchi of a patient with CF carrying the G551D and F508del CFTR mutations (G551D/F508del-HBE). In addition to the G551D CFTR gating mutation, ivacaftor increased the open probability of all other CFTR gating mutations tested, including G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. This led to a greater than 10-fold increase in chloride transport for all 10 CFTR gating mutations.

Lumacaftor partially corrects the fundamental molecular defect caused by F508del-CFTR to increase the amount of functional F508del-CFTR at the cell surface, resulting in enhanced chloride transport. The channel gating activity of F508del-CFTR delivered to the cell surface by lumacaftor can be potentiated by ivacaftor to further enhance chloride transport. When added to F508del/F508del-HBE, the magnitude of chloride transport observed with the combination of lumacaftor and either acute or chronic ivacaftor treatment was greater than that observed with lumacaftor alone.

Primary and Secondary pharmacology

Study 101 was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose, multi-center, dose-finding Phase 2a study of orally-administered VX-809 in subjects with CF. Enrolment was planned at approximately 20 centres, and approximately 90 adult subjects who were homozygous for the F508del-CFTR (previously referred to as the ΔF508-CFTR) mutation were to be enrolled.

The study had 2 cohorts:

Group A: Group A (45 subjects) was screened and randomized to receive either 25 mg of VX-809 (18 subjects), 50 mg of VX-809 (18 subjects), or placebo (9 subjects) for 28 days.

Group B: Group B (45 new subjects) was screened and randomized to receive either 100 mg of VX-809 (18 subjects), 200 mg of VX-809 (18 subjects), or placebo (9 subjects) for 28 days

Assessments included PK, Nasal potential difference (NPD), sweat chloride, spirometry (FEV1, forced vital capacity [FVC], and forced expiratory flow over the middle half of the FVC [FEF25-75]), Cystic Fibrosis Questionnaire – Revised (CFQ-R) and safety.

Nasal potential difference (NPD): At Day 28, mean changes from baseline and differences from placebo in zero chloride plus isoproterenol response of the NPD were not statistically significant for any VX-809 treatment group

Sweat chloride: Reductions from baseline in mean sweat chloride were observed as early as Day 7 in the 50, 100, and 200 mg VX-809 groups and tended to be largest in the 200 mg group. The magnitude of decreases in these 3 groups did not increase with time, and the decreases were not sustained at Day 7 follow-up. No mean decreases from baseline were seen in the 25 mg group. Mean changes in sweat chloride from baseline to Day 28 were statistically significant in the 100 mg VX-809 (-5.29 mmol/L; P=0.0173) and 200 mg (-7.38 mmol/L; P=0.0008) groups. The differences between these treatment groups and the placebo group for the least squares mean change from baseline were also statistically significant: -6.13 mmol/L (P=0.0498) for the 100 mg group and -8.21 mmol/L (P=0.0092) for the 200 mg group. The linear trend was statistically significant (-2.099; P=0.0013), suggesting a decreasing mean average sweat chloride with increasing dose.

FEV1: Results of the ANCOVA analysis of change and percent change from baseline to Day 28 in FEV1 showed no statistically significant results for either change from baseline, percent change from baseline, or difference between treatment and placebo for any VX-809 treatment group.

CFQ-R: For the CFQ-R results, at Day 28, the mean change in respiratory domain score in the placebo group was +4.5; in the VX-809 25-, 50-, 100-, and 200-mg treatment groups, the mean changes were –5.2, –6.3, –1.30, and +2.2, respectively. There were no clear or sustained improvements (i.e., increase in score of ≥5 points, the minimal clinically important difference) in the respiratory domain or in any other domains of the CFQ-R in any dose group over time.

Study 102 was a Phase 2, multicenter, double-blind, placebo-controlled, multiple-dose study of lumacaftor monotherapy, and lumacaftor and ivacaftor combination therapy in subjects with CF homozygous or heterozygous for the F508del-CFTR mutation. There were approximately 293 patients in this study who were evaluated in four different cohorts. In all the treatment cohorts, patients were treated with lumacaftor monotherapy for the first few days (14-28 days depending on the cohort) followed immediately by combination therapy with lumacaftor/ivacaftor for further 7-28 days. As there was no wash-out between monotherapy and combination therapy, a clear base-line value for the patients prior to the combination therapy is not available and makes it difficult to interpret accurately the effects of the combination.

Assessments included safety, PK, sweat chloride tests, spirometry measurements (FEV1; forced vital capacity [FVC]; forced expiratory flow midexpiratory phase [FEF25%-75%]; forced expiratory volume (L) in 1 second over forced vital capacity [FEV1/FVC)]); CFQ-R (Cohort 2, Cohort 3, and Cohort 4); and for Cohort 4 only, body mass index (BMI) and weight. There were no PD studies of the combination that included assessment of NPD or parameters related to the gastrointestinal manifestations of cystic fibrosis (except in cohort 4).

Lumacaftor monotherapy

Sweat Chloride: Reductions in mean sweat chloride values from baseline were observed beginning at Day 14 (first scheduled visit after first dose of study drug) in homozygous subjects who received lumacaftor monotherapy. At Day 14, all active treatment groups had a statistically significant within-group mean reduction from baseline in sweat chloride values. Homozygous subjects who received LUM 600 mg qd had the largest adjusted mean reduction from baseline at Day 14 (-9.363 mmol/L, P<0.001). Compared to the monotherapy placebo group, the treatment difference in the mean change from baseline at Day 14 in

homozygous subjects who received LUM 600 mg qd was -9.294 mmol/L (P = 0.005). Homozygous subjects who received LUM 400 mg q12h had an adjusted mean reduction from baseline at Day 14 of -9.014 mmol/L (P<0.007). Compared to the monotherapy placebo group, the treatment difference in the mean change from baseline at Day 14 in homozygous subjects who received LUM 400 mg q12h was -8.944 mmol/L (P = 0.028). While these effects were statistically significant, in the context of correction of CFTR function the effect-size is not of a clinically relevant magnitude.

Spirometry: No improvements in percent predicted FEV1 from baseline at Day 28 were observed in any of the active treatment groups during the monotherapy period.

CFQ-R: A statistically significant within group adjusted mean absolute change from baseline at Day 28 in CFQ-R respiratory domain score was observed in the LUM 600 mg qd and LUM 400 mg q12h homozygous groups (with the largest change in the LUM 600 mg qd group [-9.8 points, P = 0.006]), and the LUM 600 mg qd heterozygous group (-9.1 points, P = 0.006).

Lumacaftor and ivacaftor combination therapy

Sweat Chloride: There were no statistically significant differences in the mean changes or the treatment effect between the active treatment groups compared to the placebo group for the mean absolute change from Day 28 at Day 56 in sweat chloride values. The observed changes in sweat chloride values during the monotherapy period were generally maintained during the combination therapy period, with little change following the addition of ivacaftor. A statistically significant within-group adjusted mean absolute change from baseline at Day 56 (entire treatment period) in sweat chloride values was observed in all active treatment groups, with the LUM 400 mg q12h/IVA 250 mg q12h homozygous group having the largest within-group adjusted mean absolute change (-10.432 mmol/L, P = 0.001). The treatment difference for the LUM 400 mg q12h/IVA 250 mg q12h homozygous group compared to the pooled combination placebo group in the mean absolute change from baseline at Day 56 was -10.990 mmol/L (95% CI: -18.299, -3.682), which was statistically significant (P = 0.004). The LUM 600 mg qd/IVA 250 mg q12h homozygous group had a within-group adjusted mean absolute change of -8.970 mmol/L (P<0.001). The treatment difference for the LUM 600 mg qd/IVA 250 mg q12h homozygous group compared to the pooled combination placebo group in the mean absolute change from baseline at Day 56 was -9.528 mmol/L (95% CI: -15.124, -3.932), which was statistically significant (P = 0.001).

Spirometry: Subjects who received active treatment with combination (lum/iva) had improvements in percent predicted FEV1 when compared with lumacaftor monotherapy for 28 days. The largest within-group improvements in the mean absolute change in percent predicted FEV1 from Day 28 at Day 56 were observed in homozygous subjects who received LUM 600 mg qd in combination with IVA 250 mg q12h (6.20 percentage points; P<0.001) and LUM 400 mg q12h in combination with IVA 250 mg q12h (6.16 percentage points; P = 0.005). Compared to the pooled combination placebo group, the treatment difference in the mean absolute change from Day 28 at Day 56 was 7.77 percentage points (P<0.001) for homozygous subjects who received LUM 600 mg qd in combination with IVA 250 mg q12h and 7.72 percentage points (P = 0.003) for homozygous subjects who received LUM 400 mg q12h in combination with IVA 250 mg q12h. Improvements from baseline in percent predicted FEV1 at the end of the treatment period (Day 56) were observed in homozygous subjects. Subjects receiving LUM 600 mg qd followed by LUM 600 mg qd in combination with IVA 250 mg q12h had the largest within-group improvement in the mean absolute change from baseline at Day 56 in percent predicted FEV1 (3.56 percentage points, P = 0.030). Compared to the pooled combination placebo group, the treatment difference in the mean absolute change from baseline at Day 56 was 5.59 percentage points (P = 0.014) for these subjects. Subjects receiving LUM 400 mg q12h followed by LUM 400 mg q12h in combination with IVA 250 mg q12h had a within-group mean absolute change from baseline at Day 56 of 2.13 percentage points (P = 0.354) and a treatment difference compared to the pooled combination placebo group of 4.16 percentage points (P = 0.137).

CFQ-R: Statistically significant within group adjusted mean absolute change from baseline at Day 28 in CFQ-R respiratory domain score was observed in the LUM 600 mg qd and LUM 400 mg q12h homozygous groups (with the largest change in the LUM 600 mg qd group [-9.8 points, P = 0.006]), and the LUM 600 mg qd heterozygous group (-9.1 points, P = 0.006). Statistically significant within group adjusted mean absolute change from Day 28 at Day 56 in CFQ-R respiratory domain score was observed in the LUM 400 mg q12h/IVA 250 mg q12h homozygous group (11.3 points, P = 0.033), the LUM 600 mg qd/IVA 250 mg q12h homozygous group (9.1 points, P = 0.016), and the LUM 400 mg qd/IVA 250 mg q12h homozygous group (8.2 points, P = 0.030).

Based on the above results, a consistent pattern as observed with ivacaftor monotherapy in G551D patients was not observed. Due to the study design of study 102, a clear interpretation on the effects of combination cannot be made. Therefore progressing to phase 3 studies on this data is associated with significant risk; however it is agreed that if a positive decision was to be made on starting phase 3 studies with this data, the dose-regimens of lum 400mg bd/iva 250 mg bd and lum 600mg qd/iva 250mg bd are the most promising to carry-forward.

There are no specific secondary pharmacology studies except the investigation of the effects of the combination lum/iva on QTc. The upper limit of the 2-sided 90% CI for the least squares (LS) mean difference from placebo for the time-matched, baseline-adjusted QTcF interval for both the therapeutic and supratherapeutic dose regimens did not exceed 10 msec, indicating that lumacaftor and ivacaftor combination therapy does not prolong the QTc interval to a clinically significant degree at the therapeutic and supratherapeutic dose levels. The lower limit of the 2-sided 97.5% CI for the LS mean difference from placebo for the baseline-adjusted QTcF interval for moxifloxacin ranged from 0.0 to 3.0 msec. The lower limit did not exceed 5 msec at any time point, indicating that assay sensitivity was not demonstrated according to the criteria specified in the protocol. It is noted that the mean Cmax (1.94 µg/mL) and AUC0-24h (20.3 µg.h/mL) were lower as compared to the moxifloxacin Cmax and AUC0-24h in the manufacturer's label 3.1 µg/mL for Cmax and 36.1 µg·h/mL for AUC0-24h following a single oral dose of moxifloxacin 400 mg, as moxifloxacin was dosed with food in the current study. Further assay sensitivity was established according to ICH E14 criteria via an ad-hoc analysis. Moreover it is seen that the effect of lum/iva on QTc is predominantly to reduce the QTc interval rather than prolong it even at the supra-therapeutic dose as shown in the figure below. Further the clinical experience with lum/iva has not raised any significant cardiac safety signals.

PK-PD modelling

The PKPD modelling shows a linear relationship for FEV1 and lumacaftor concentration. It was concluded that it was not possible to study the effects of the mono-components in the model. The effect on FEV1 appears moderate and the effect of the covariates does not appear to be significant. It is considered an omission that the effect of the two components could not be distinguished in the model as this would have provided useful supporting data for the combination and the exposure of ivacaftor.

2.4.4. Discussion on clinical pharmacology

A full characterisation of the pharmacokinetics of both the individual components lumacaftor and ivacaftor as well as that of the fixed dose combination has been provided. Lumacaftor and ivacaftor are both low solubility compounds. Intravenous data is not available therefore high absorption cannot be assumed but both components are absorbed following oral dosing and pharmacokinetics of lumacaftor are linear over the dose range of 50- 600 mg. High fat food increases the exposure of both lumacaftor and ivacaftor in healthy volunteers although timing of the food has not been investigated. The mean protein binding values of [14C]-lumacaftor ranged from 99.97% to 100.00% in human plasma and is predominantly to albumin. Ivacaftor, M1-ivacaftor, and M6-ivacaftor were highly bound (>98%) to proteins in human

plasma at all concentrations tested. Ivacaftor protein binding to human plasma components, HSA, AAG and HGG was greater than 97%, suggesting that ivacaftor was highly bound to most of the proteins of human plasma. M1-ivacaftor and M6-ivacaftor were highly (>99%) bound to HSA with low binding to AAG and HGG.

The major route of elimination of lumacaftor was unchanged lumacaftor in faeces. Lumacaftor is metabolised by oxidation and glucuronidation however these do not appear to be major elimination pathways. The major circulating metabolite for lumacaftor is M28 but it is claimed that this is less than 10% at steady state concentrations. Ivacaftor is extensively metabolised predominantly by CYP 3A4. M1-ivacaftor and M6-ivacaftor are the 2 major circulating metabolites of ivacaftor. The pharmacokinetics of lumacaftor appears to be essentially time independent. Population pharmacokinetics was performed to identify PKPD relationships in the phase III studies. The demographics of the data were limited and did not allow for exploration of race other than white or of age above 57 years. Age and weight were significant covariates in the model while gender did not have an effect. A study performed in moderately hepatic impaired patients showed a 50% and 30% increase in exposure, for Cmax and AUC respectively. No adjustment in mild impairment is proposed, however the suggested dose in severely impaired patients needs to be amended, as per the guidance given in the SmPC.

Lumacaftor is an inducer of CYP 3A4, 2B6, 2C9 and 2C19, it does not induce CYP1A2. The M28 metabolite of lumacaftor does not induce CYP 3A4. Lumacaftor is an inhibitor of CYP 2C8 and a weak inhibitor of 2C9. No time dependency was seen. Ivacaftor also inhibits 2C8, is a weak inhibitor of CYP 2C9.

The PK of lumacaftor and ivacaftor were comparable on coadministration with the various bronchodilators used in the study and ciprofloxacin had only a minimal effect on lumacaftor and caused a 28% increase in the exposure of ivacaftor. A prototypical probe study for the effect of lumacaftor on a CYP3A substrate such as midazolam was not conducted due to the fact that ivacaftor is a sensitive CYP3A substrate, which showed the expected large effect with substantial reductions in exposure due to lumacaftor induction. Itraconazole had no effect on the PK of lumacaftor and M28-lumacaftor, but caused a substantial increase in the exposure of ivacaftor when given in combination with lumacaftor. A lower magnitude of increase was observed in the exposures of M1-ivacaftor in the presence of itraconazole; however, there was no change in the exposure of M6-ivacaftor. Rifampin altered the shape of the concentration time profile of lumacaftor but had no substantial impact on the overall exposure. M28-lumacaftor exposures mildly increased in the presence of rifampin. Rifampin induces the metabolism of CYP3A; when given in combination with rifampin, the exposures of ivacaftor substantially decreased, M1-ivacaftor exposure mildly decreased, and M6-ivacaftor mildly increased. Based on these results, coadministration of lumacaftor and ivacaftor combination therapy with rifampin or any strong inducer of CYP3A is not recommended because ivacaftor exposure will be decreased, which may lead to loss of efficacy. Considering that lumacaftor is a potent inducer of CYP3A4, and that for CYP2C8 and CYP2C9 substrates the interaction is unknown because the effect of lumacaftor + ivacaftor may also be affected by the inhibition of CYP2C8 by lumacaftor and CYP2C9 by both lumacaftor and ivacaftor as observed in vitro, the CHMP requested detailed information in the SmPC on the concomitant use of Orkambi with CYP450 substrates along with explanation of measures to be taken (e.g. monitoring) in cases when co-administration is required, which was included in the SmPC by the applicant.

The exposure of ivacaftor (250mg BD) when combined with lumacaftor is lower than the exposure of ivacaftor (150mg BD) when used alone despite the higher dose used. However the adequacy of this dose in the combination is supported by in-vitro data which shows that F508del-CFTR cells are 10 times more sensitive than the G551D-CFTR cells. However, at the proposed higher dose of ivacaftor, the concentrations of the M6 metabolite are higher than in the monotherapy programme and as compared to those seen in non-clinical studies. It is considered that receptor binding and ion channel assays to assess the potential for off-target activity should be provided for this metabolite to provide reassurance. This will be performed as a post authorisation study as described in the RMP.

The mechanism of action of lumacaftor/ivacaftor in the target population is based mainly on in-vitro studies. Lumacaftor is an F508del-CFTR corrector. In human bronchial epithelial cells from CF patients with homozygous F508del-CFTR, lumacaftor enhanced chloride transport by facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of functional CFTR protein at the cell surface. Ivacaftor is a CFR potentiator that increases the channel activity of the CFTR protein located at the cell surface. It also increases chloride transport in HBE cells from CF patients carrying the G551D/F508del mutation. The combination of lum/iva has higher magnitude of chloride transport as compared to lumacaftor alone in F508del/F508del-HBE cells.

In pharmacodynamics with lumacaftor monotherapy and lum/iva combination, ivacaftor showed a consistent effect on NPD, sweat chloride and lung function, while lumacaftor monotherapy showed an effect only on sweat chloride. The magnitude of this effect is not considered clinically relevant in the context of CF. The combination seemed to maintain the effect of lumacaftor monotherapy on sweat chloride and showed an improvement in lung function (FEV1) especially at the lum 600mg qd/iva 250mg bd and lum 400mg bd/iva 250mg bd dose regimens.

Though the QTc study did not formally demonstrate adequate assay sensitivity, the overall results is considered sufficiently reassuring that the risk of QTc prolongation with lum/iva is negligible.

2.4.5. Conclusions on clinical pharmacology

The PK of Orkambi was mainly characterised in healthy volunteer studies, which is acceptable since CF is a rare disease. This has been complemented with sufficient PK characterisation in the CF patients in phase II/III studies. The exposures of lumacaftor are approximately 2-fold higher in healthy adult volunteers compared to subjects with CF. The pharmacokinetics of ivacaftor, when administered with lumacaftor, is similar between healthy adult volunteers and subjects with CF. Both lumacaftor and ivacaftor are low solubility compounds but are absorbed following oral dosing. The PK of lumacaftor is linear in the dose range of 50-1000 mg every 24 hours and the PK of ivacaftor is shown to be linear in the range of 150 mg to 250 mg every 12 hours. High fat food increases the exposure of both lumacaftor and ivacaftor. The median tmax of lumacaftor and ivacaftor is approximately 4 hours in the fed state. Both lumacaftor and ivacaftor are extensively bound to plasma proteins, with lumacaftor binding to albumin and ivacaftor to alpha-1-glycoprotein & albumin.

Lumacaftor is not extensively metabolised in humans with majority of the drug excreted unchanged in the faeces. The apparent terminal half-life is 26 hours. The main metabolic pathway is via oxidation and glucoronidation. Ivacaftor is extensively metabolised primarily by CYP3A. M1 and M6 are active metabolites, with M1 having 1/6th the potency and M6 having 1/50th the potency of ivacaftor. Majority of the ivacaftor is eliminated in the faeces after metabolic conversion. In patients with moderate hepatic impairment, the exposure of both lum and iva is increased and hence a dose-reduction is advised in the SmPC. Lumacaftor is a CYP3A inducer and hence the exposure of ivacaftor is lowered at steady state when administered as a combination with lumacaftor. Hence the dose of ivacaftor (250mg bd) is higher in the combination regimen as compared to the ivacaftor monotherapy (150mg bd). Ivacaftor and/or lumacaftor were shown to have a large potential for interacting with other medicinal products and hence, the CHMP requested detailed information in the SmPC on the concomitant use of Orkambi with other medicines, which was implemented by the applicant. The measures to be taken in cases when co-administration is required are also included.

In PD studies, lumacaftor monotherapy had a significant, but not clinically relevant effect on sweat chloride which was maintained by the combination lum/iva. There was no additional effect on sweat chloride when luma/iva was administered to patients after receiving lumacaftor monotherapy for 28 days. Lumacaftor monotherapy caused a dose-dependent decline in FEV1. However, when the combination of

lum/iva was administered subsequent to lumacaftor monotherapy, there was a reversal of the decline in FEV1 and an increase in FEV1 from the baseline was also seen. It is pertinent to note here that ivacaftor monotherapy when evaluated in CF patients with G551D defect, had a consistent and significant effect on NPD, sweat chloride and FEV1.

Overall, the pharmacology of the FDC and the single compounds is considered sufficiently characterised for marketing authorisation.

2.5. Clinical efficacy

2.5.1. Dose response study

The dose-selection of the combination was based on the results of the study 102 which was discussed under pharmacodynamics. Study 102 was a Phase 2, multicenter, double-blind, placebo-controlled, multiple-dose study of lumacaftor monotherapy, and lumacaftor and ivacaftor combination therapy in subjects with CF who are homozygous or heterozygous for the F508del-CFTR mutation. The primary objective of this study was to evaluate the PK, safety and tolerability when is administered alone or in combination with ivacaftor and to evaluate the effect of lumacaftor administered alone or in combination with ivacaftor on sweat chloride. Two dose regimens lum 600mg qd/iva 250mg bd and lum 400mg bd/iva 250 mg bd were selected for phase III studies.

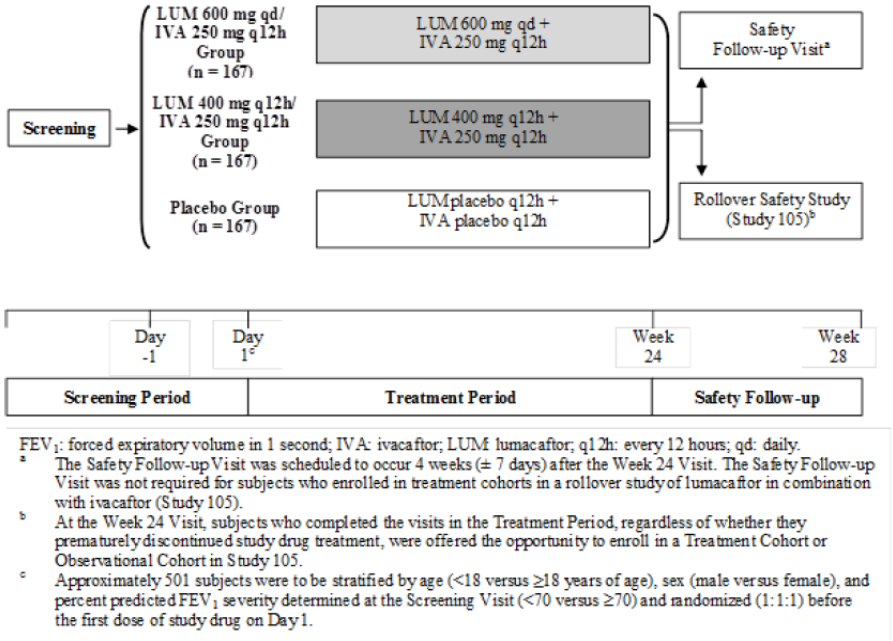
2.5.2. Main studies

Pivotal Phase 3 studies VX12-809-103 (Study 103) and VX12-809-104 (Study 104) were randomized, double-blind, placebo-controlled, parallel-group studies that evaluated lumacaftor in combination with ivacaftor in subjects aged 12 years and older with CF who are homozygous for the F508del-CFTR mutation.

Methods

Studies 103 and 104 were similar in study design, population, and treatment regimens. Both studies evaluated 2 dosing regimens of lumacaftor (LUM 600 mg qd and LUM 400 mg q12h) in combination with ivacaftor (IVA 250 mg q12h) across 24 weeks. Treatment with lumacaftor and ivacaftor or placebo was administered in addition to the subject's usual prescribed CF therapy. The study treatments were to be administered within 30 minutes of consuming fat containing food to enhance and ensure sufficient systemic exposure.

Schematic of the Study Design (103 and 104)



FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

[a] The Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the Week 24 Visit. The Safety Follow-up Visit was not required for subjects who enrolled in treatment cohorts in a rollover study of lumacaftor in combination with ivacaftor (Study 105).

[b] At the Week 24 Visit, subjects who completed the visits in the Treatment Period, regardless of whether they prematurely discontinued study drug treatment, were offered the opportunity to enroll in a Treatment Cohort or Observational Cohort in Study 105.

[c] Approximately 501 subjects were to be stratified by age (<18 versus ≥18 years of age), sex (male versus female), and percent predicted FEV_1 severity determined at the Screening Visit (<70 versus ≥70) and randomized (1:1:1) before the first dose of study drug on Day 1.

Study Participants

Studies 103 and 104 were sponsored by Vertex and subjects were randomized at 96 (Study 103) and 91 (Study 104) sites in North America, Europe, and Australia.

Both studies recruited subjects aged 12 years and above with a confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis or 2 CF-causing mutations and either chronic sinopulmonary disease, or gastrointestinal/ nutritional abnormalities were recruited. Enrolment was limited to subjects who had a FEV1 ≥40 and ≤90 percent of predicted normal.

Outcomes/endpoints

The primary efficacy endpoint in both studies was the absolute change from baseline in percent predicted FEV1 (with a unit of percentage points) at Week 24. Percent predicted FEV1 was the ratio of FEV1 (L) to the predicted FEV1 (L), expressed as a percentage.

The secondary efficacy endpoints were:

- Relative Change From Baseline in Percent Predicted FEV1 at Week 24
- Absolute Change From Baseline in BMI at Week 24
- Absolute Change From Baseline in CFQ-R Respiratory Domain Score at Week 24
- Response Defined as ≥5% Increase in Average Relative Change From Baseline in Percent Predicted FEV1 at Week 16 and at Week 24
- Number of Pulmonary Exacerbations Through Week 24

Pulmonary exacerbation was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the predefined signs/symptoms. This definition was based on the definition of a pulmonary exacerbation used in previous clinical studies, including ivacaftor clinical studies.

Additional secondary endpoints were: Absolute and relative changes from baseline of FEV1 in litres, forced vital capacity (FVC), pp FVC, forced mid-expiratory flow rate ($FEF_{25-75\%}$), pp $FEF_{25-75\%}$ and FEV1/FVC at week 24. Additional endpoints related to pulmonary exacerbation were: time-to-first

pulmonary exacerbation, the incidence of having at least 1 pulmonary exacerbation, number of days with pulmonary exacerbation, number of pulmonary exacerbation requiring hospitalization, number of days hospitalized for pulmonary exacerbation, time-to-first hospitalization for pulmonary exacerbation, number of pulmonary exacerbation requiring iv antibiotic therapy, number of days on iv antibiotic therapy for pulmonary exacerbation, and time-to-first antibiotic therapy for pulmonary exacerbation. Additional nutritional status endpoints were: absolute change from baseline in weight and in BMI for age-z-score at week 24, and absolute change from baseline in weight z-score, height z-score, and height at week 24

Sample size

The study sample size was calculated assuming an absolute change in ppFEV1 of 5% with a standard deviation of 8% for a study with 99% power to detect a 5% change between treatment arms at the 0.025 significance level from a study assuming a 10% drop-out rate. A total sample size of 501 subjects (167 subjects for each treatment group) had approximately 99% power to detect a treatment difference of 5 percentage points in absolute change of percent predicted FEV1 between either dose of lumacaftor in combination with ivacaftor compared with placebo. The study had approximately 98% power to detect a treatment difference of 6% in relative change of percent predicted FEV1 between each active treatment group and the placebo group at the 0.025 level of significance. This was based on the assumption of having a relative change in percent predicted FEV1 of 6 for the active treatment groups, an associated SD of 12%, and a sample size of 167 subjects for each treatment group (active and placebo). The assumed mean absolute/relative changes and SD were based on results from an ongoing Phase 2 study, Study 102. The power calculation was based on simulation using Splus with a 2-sided t-test for data sampled from the normal distribution.

Treatments/ Objectives

The Treatment Period lasted approximately 24 weeks. Subjects were randomized to 1 of 3 treatment groups: 2 combination treatment groups and 1 placebo group. The dosing regimen for each treatment group was as follows:

- LUM 600 mg qd/IVA 250 mg q12h
- LUM 400 mg q12h/IVA 250 mg q12h
- LUM placebo q12h/IVA placebo q12h (placebo)

Study drug was to be administered within 30 minutes of consumption of fat-containing food such as a standard “CF” high-fat, high-calorie meal or snack.

Randomisation

Subjects who met eligibility criteria were randomized (1:1:1) to 1 of 3 treatment groups. Randomization was stratified by age (<18 versus ≥18 years old), sex (male versus female), and percent predicted FEV1 severity collected at the Screening Visit (<70 versus ≥70). An interactive web response system (IWRS) was used to assign subjects to treatment.

Blinding (masking)

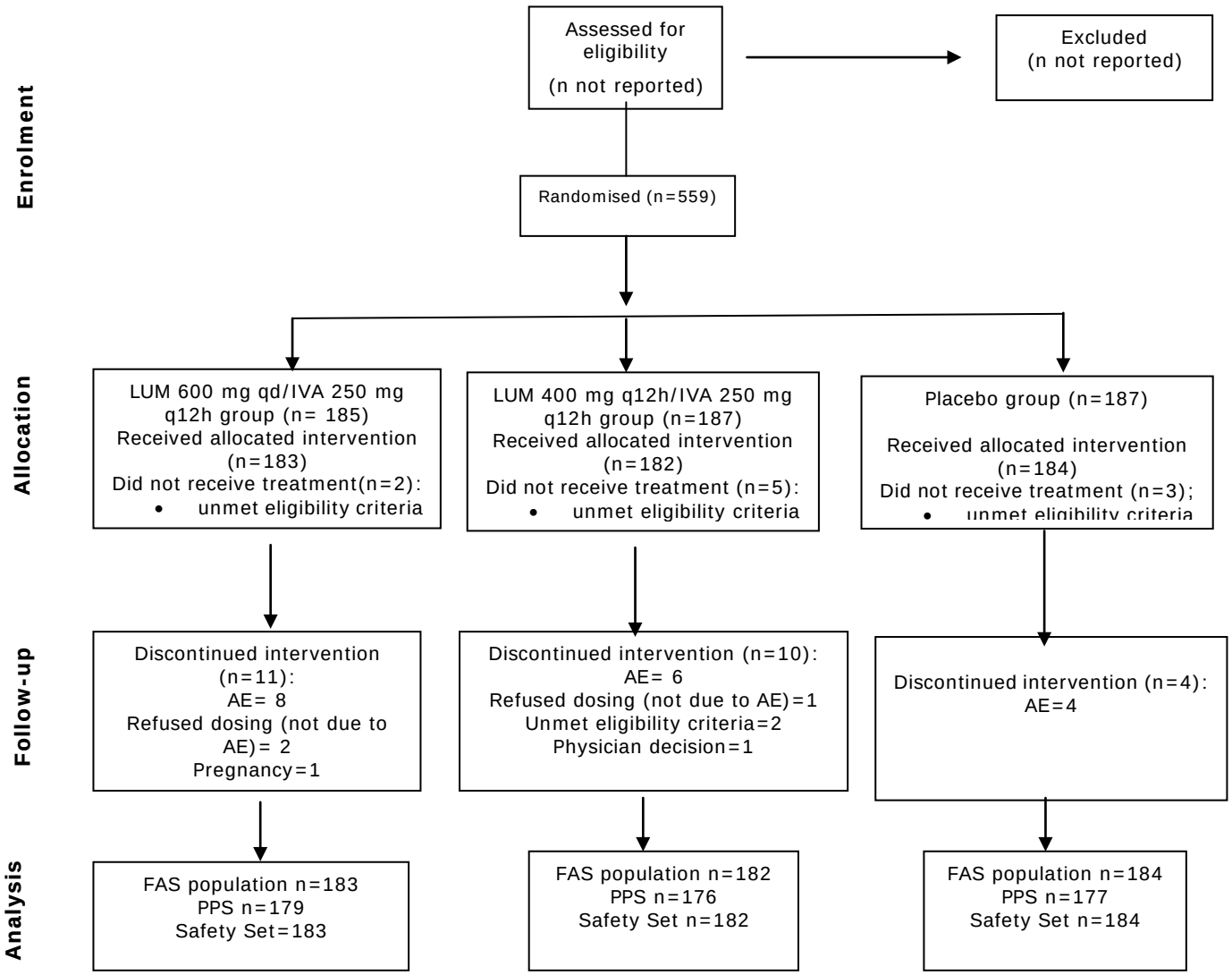
Subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded, with exception of staff acting in emergency situation to ensure safety of the patients. Subjects and their caregivers were not to be informed of their study-related spirometry results during the Treatment Period even if the subject prematurely discontinued study drug treatment.

Statistical methods

The Full Analysis Set (FAS), including all subjects who were randomised and received any amount of study drug, was used for all efficacy analyses. The primary efficacy endpoint was the absolute change from

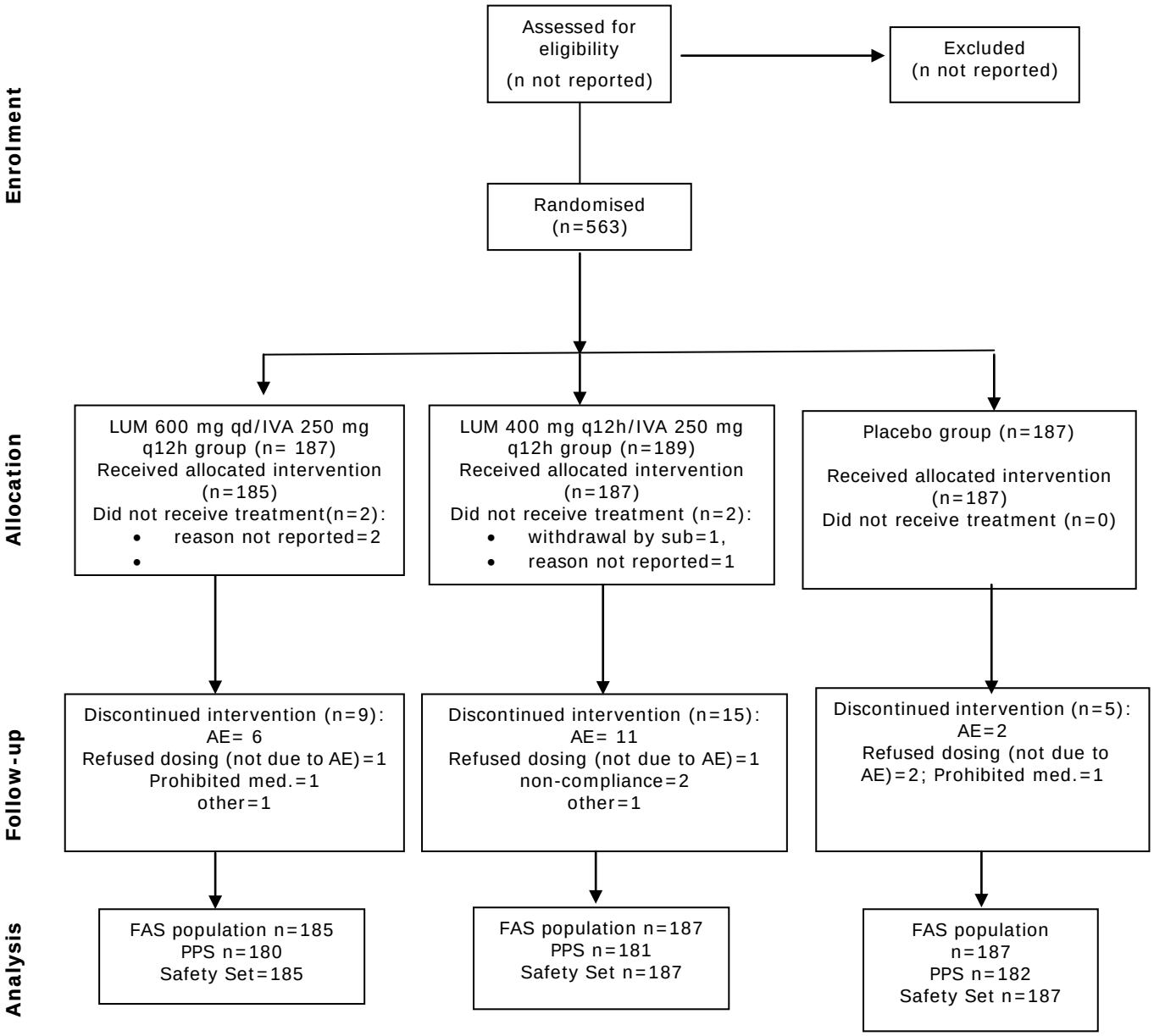
baseline in percent predicted FEV1 at Week 24, assessed as the average treatment effect at Week 16 and at Week 24. The primary analysis for this endpoint was based on a mixed-effects model for repeated measures (MMRM).

Results 103
Participant flow 103



- FAS was defined as all randomized subjects who received any amount of study drug.
- PPS was defined as all FAS subjects without important protocol deviations that may have had a substantial impact on efficacy assessments.
- Safety Set was defined as all subjects who received any amount of study drug.

Participant flow Study 104



- FAS was defined as all randomized subjects who received any amount of study drug.
- PPS was defined as all FAS subjects without important protocol deviations that may have had a substantial impact on efficacy assessments.
- Safety Set was defined as all subjects who received any amount of study drug.

Recruitment

Study VX12-809-103: The study was initiated on 28 May 2013 and completed on 29 April 2014.

Study VX12-809-104: The study was initiated on 11 April 2013 and completed on 25 April 2014.

Conduct of the study

In both studies, the total number of patients discontinuing from the study is small and the number of patients discontinuing treatment was also small in both studies. The discontinuations were much lower

than the anticipated 10% drop-out rate. This low rate of drop-outs further enhances the power of the study to reliably detect a smaller than anticipated treatment effect. The number of drop-outs are higher in the treatment groups (4.9-6.0%) as compared to the placebo group (2.2 to 2.7) in the two studies, which suggests that overall the drop-out due to lack of efficacy is negligible in the studies including in the placebo group. Most of the drop-outs have been to adverse events.

Baseline data

The baseline data in both studies were generally balanced across treatment arms. However the percentage of patients receiving inhaled antibiotics was 66.3% in placebo, 59.6% in lum 600mg qd/iva 250 mg bd and 62.1% in lum 400mg bd/iva 250 mg bd in study 103. In study 104, this was 72.7% in placebo, 66.5% in lum 600mg qd/ iva 250 mg bd and 59.9% in lum 400mg bd/iva 250 mg bd. As the definition of pulmonary exacerbation, a key secondary endpoint depends on the change in antibiotics, the higher use of antibiotics at baseline may suggest a population of higher risk of exacerbations. It is observed that the number of patients on inhaled antibiotics is relatively larger in the placebo group as compared to the treatment groups in both the studies. Further it is noted that in study 104, the baseline use of inhaled antibiotics was lowest in the lum 400mg bd/iva 250mg bd. It is possible that higher level of baseline antibiotic use reflects a patient population who are at higher risk of infection and subsequent risk of exacerbations. However as the applicant pointed out, the higher use of antibiotics in a particular treatment arm could also result in lesser number of exacerbations in that arm. It is agreed that a definitive conclusion cannot be made on the way this small imbalance in baseline use of antibiotics can impact on the observed results.

Numbers analysed

Study VX12-809-103: Approximately 501 subjects were planned to be randomized (167 subjects in each treatment group). A total of 559 subjects were randomized: 185 subjects to LUM 600 mg qd/IVA 250 mg q12h, 187 subjects to LUM 400 mg q12h/IVA 250 mg q12h, and 187 subjects to placebo. A total of 549 subjects received at least 1 dose of study drug (LUM/IVA or placebo). The number of subjects in each analysis set is provided in the table below:

Analysis Populations

	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg q12h/ IVA 250 mg q12h	LUM/IVA Total	Overall
All Subjects Set	187	185	187	372	559
Full Analysis Set	184	183	182	365	549
Safety Set	184	183	182	365	549

IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

Note: All Subjects Set: all subjects in the study who were randomized or dosed (received any amount of study drug); Safety Set: all subjects who received any amount of study drug; Full Analysis Set: all randomized subjects who received any amount of study drug.

Study VX12-809-104: Approximately 501 subjects were planned to be randomized (167 in each treatment group). A total of 563 subjects were randomized: 187 to LUM 600 mg qd/IVA 250 mg q12h, 189 to LUM 400 mg q12h/ IVA 250 mg q12h, and 187 to placebo. A total of 559 subjects received at least 1 dose of study drug (LUM/IVA or placebo). The number of subjects in each analysis set is provided in the table below:

Analysis Populations

	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg q12h/ IVA 250 mg q12h	LUM/IVA Total	Overall
All Subjects Set	187	187	189	376	563
Full Analysis Set	187	185	187	372	559
Safety Set	186	186	187	372	559

FAS: Full Analysis Set; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

Note: All Subjects Set: all subjects in the study who were randomized or dosed; Safety Set: all subjects who received any amount of study drug; FAS: all randomized subjects who received any amount of study drug. The Safety Set included 1 less subject (Subject XXXX) in the placebo group and 1 additional subject (Subject XXXX) in the LUM 600 mg qd/IVA 250 mg q12h group compared with the FAS because 2 subjects received the wrong study drug during the study and were assigned to the active treatment group with the lowest dosage that they received (Subject XXXX shifted from the placebo group to the LUM 400 mg q12h/IVA 250 mg q12h group, and Subject XXXX shifted from the LUM 400 mg q12h/ IVA 250 mg q12h group to the LUM 600 mg qd/ IVA 250 mg q12h group).

Outcomes and estimation

The comparative results across the two pivotal studies and the results from the pooled data of both the pivotal studies for the primary endpoint and the key secondary endpoint are presented in the tables below.

Studies 103 and 104: Primary and Key Secondary Efficacy Analysis, Full Analysis Set

	Study 103			Study 104			Pooled Studies 103 and 104		
Analysis Statistic	Placebo N = 184	LUM 600 mg qd/ IVA 250 mg q12h N = 183	LUM 400 mg q12h/ IVA 250 mg q12h N = 182	Placebo N = 187	LUM 600 mg qd/ IVA 250 mg q12h N = 185	LUM 400 mg q12h/ IVA 250 mg q12h N = 187	Placebo N = 371	LUM 600 mg qd/ IVA 250 mg q12h N = 368	LUM 400 mg q12h/ IVA 250 mg q12h N = 369
Primary: Average absolute change from baseline in percent predicted FEV_1 at Week 16 and at Week 24									
Within-group change (SE)	-0.44 (0.524) *P* = 0.4002	3.59 (0.525) *P*<0.0001	2.16 (0.530) *P*<0.0001	-0.15 (0.539) *P* = 0.7744	2.46 (0.540) *P*<0.0001	2.85 (0.540) *P*<0.0001	-0.32 (0.376) *P* = 0.3983	3.00 (0.377) *P*<0.0001	2.49 (0.379) *P*<0.0001
Treatment difference (95% CI)	NA	4.03 (2.62, 5.44) *P*<0.0001	2.60 (1.18, 4.01) *P* = 0.0003	NA	2.62 (1.18, 4.06) *P* = 0.0004	3.00 (1.56, 4.44) *P*<0.0001	NA	3.32 (2.31, 4.33) *P*<0.0001	2.81 (1.80, 3.82) *P*<0.0001
Key Secondary: Average relative change from baseline in percent predicted FEV_1 at Week 16 and at Week 24									
Within-group change (SE)	-0.34 (0.913) *P* = 0.7113	6.39 (0.914) *P*<0.0001	3.99 (0.923) *P*<0.0001	0.00 (0.960) *P* = 0.9983	4.42 (0.961) *P*<0.0001	5.25 (0.961) *P*<0.0001	-0.17 (0.662) *P* = 0.8030	5.40 (0.663) *P*<0.0001	4.64 (0.666) *P*<0.0001
Treatment difference (95% CI)	NA	6.73 (4.27, 9.19) *P*<0.0001	4.33 (1.86, 6.80) *P* = 0.0006	NA	4.42 (1.86, 6.98) *P* = 0.0007	5.25 (2.69, 7.81) *P*<0.0001	NA	5.56 (3.79, 7.34) *P*<0.0001	4.81 (3.03, 6.59) *P*<0.0001
Key Secondary: Response defined as ≥5% increase in average relative change from baseline in percent predicted FEV_1 at Week 16 and at Week 24									
Yes, n (%)	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)	83 (22.4)	170 (46.2)	144 (39.0)
No, n (%)	143 (77.7)	98 (53.6)	115 (63.2)	145 (77.5)	100 (54.1)	110 (58.8)	288 (77.6)	198 (53.8)	225 (61.0)
Odds ratio (95% CI)	NA	2.9378 (1.8786, 4.5941) *P*<0.0001[a]	2.0592 (1.2920, 3.2819) *P* = 0.0023[a]	NA	2.9568 (1.8829, 4.6431) *P*<0.0001[a]	2.3834 (1.5234, 3.7286) *P* = 0.0001[a]	NA	2.9472 (2.1452, 4.0490) *P*<0.0001	2.2227 (1.6098, 3.0691) *P*<0.0001
Key Secondary: Number of pulmonary exacerbations through Week 24									
Number of events (event per year)	112 (1.07)	79 (0.77)	73 (0.71)	139 (1.18)	94 (0.82)	79 (0.67)	251 (1.14)	173 (0.80)	152 (0.70)
Rate ratio (95% CI)	NA	0.7186 (0.5170, 0.9987) *P* = 0.0491	0.6643 (0.4749, 0.9291) *P* = 0.0169[a]	NA	0.6912 (0.5187, 0.9209) *P* = 0.0116[a]	0.5659 (0.4191, 0.7641) *P* = 0.0002[a]	NA	0.7014 (0.5642, 0.8718) *P* = 0.0014	0.6095 (0.4868, 0.7630) *P*<0.0001

Studies 103 and 104: Primary and Key Secondary Efficacy Analysis, Full Analysis Set

Analysis Statistic	Study 103 Placebo N = 184	Study 103 LUM 600 mg qd/ IVA 250 mg q12h N = 183	Study 103 LUM 400 mg q12h/ IVA 250 mg q12h N = 182	Study 104 Placebo N = 187	Study 104 LUM 600 mg qd/ IVA 250 mg q12h N = 185	Study 104 LUM 400 mg q12h/ IVA 250 mg q12h N = 187	Pooled Studies 103 and 104 Placebo N = 371	Pooled Studies 103 and 104 LUM 600 mg qd/ IVA 250 mg q12h N = 368	Pooled Studies 103 and 104 LUM 400 mg q12h/ IVA 250 mg q12h N = 369
Key Secondary: Absolute change from baseline in BMI at Week 24									
Within-group change (SE)	0.19 (0.070) $P = 0.0065$	0.35 (0.070) $P<0.0001$	0.32 (0.071) $P<0.0001$	0.07 (0.066) $P = 0.2892$	0.48 (0.066) $P<0.0001$	0.43 (0.066) $P<0.0001$	0.13 (0.048) $P = 0.0066$	0.41 (0.049) $P<0.0001$	0.37 (0.048) $P<0.0001$
Treatment difference (95% CI)	NA	0.16 (-0.04, 0.35) $P = 0.1122$	0.13 (-0.07, 0.32) $P = 0.1938$	NA	0.41 (0.23, 0.59) $P<0.0001$	0.36 (0.17, 0.54) $P = 0.0001$	NA	0.28 (0.15, 0.41) $P<0.0001$	0.24 (0.11, 0.37) $P = 0.0004$
Key Secondary: Absolute change from baseline in CFQ-R respiratory domain at Week 24									
Within-group change (SE)	1.10 (1.161) $P = 0.3423$	4.98 (1.178) $P<0.0001$	2.60 (1.192) $P = 0.0295$	2.81 (1.153) $P = 0.0152$	5.02 (1.166) $P<0.0001$	5.66 (1.169) $P<0.0001$	1.88 (0.818) $P = 0.0213$	4.94 (0.828) $P<0.0001$	4.10 (0.834) $P<0.0001$
Treatment difference (95% CI)	NA	3.88 (0.70, 7.05) $P = 0.0168$*	1.50 (-1.69, 4.69) $P = 0.3569$	NA	2.21 (-0.91, 5.33) $P = 0.1651$	2.85 (-0.27, 5.98) $P = 0.0736$	NA	3.06 (0.83, 5.28) $P = 0.0071$	2.22 (-0.01, 4.45) $P = 0.0512$

BMI: body mass index; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; NA: not applicable; SE: standard error; q12h: every 12 hours; qd: once daily.

Notes: Within each treatment group for Studies 103 and 104, the treatment difference was considered statistically significant if $P \leq 0.0250$, and if all previous tests within the testing hierarchy also met this level of significance. The testing hierarchy was as follows: (1) absolute change from baseline in percent predicted FEV_1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24, (2) relative change from baseline in percent predicted FEV_1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24, (3) absolute change from baseline in BMI at Week 24, (4) absolute change from baseline in the CFQ-R respiratory domain score at Week 24, (5) response defined as ≥5% increase in average relative change from baseline in percent predicted FEV_1 at Week 16 and at Week 24, and (6) number of pulmonary exacerbations through Week 24. For the analysis of pooled data from Studies 103 and 104, a testing hierarchy was not applied, and the treatment difference was considered statistically significant if $P \leq 0.0250$.

* P value was ≤0.0250; however, it was not considered statistically significant within the framework of the testing hierarchy.

It should be noted that the spirometry results presented in the above table is the change from baseline of an average of the results from week 16 and week 24. The results of the absolute change in ppFEV1 (primary endpoint) from baseline to week 24 in both the studies and the pooled analysis are presented in the table below.

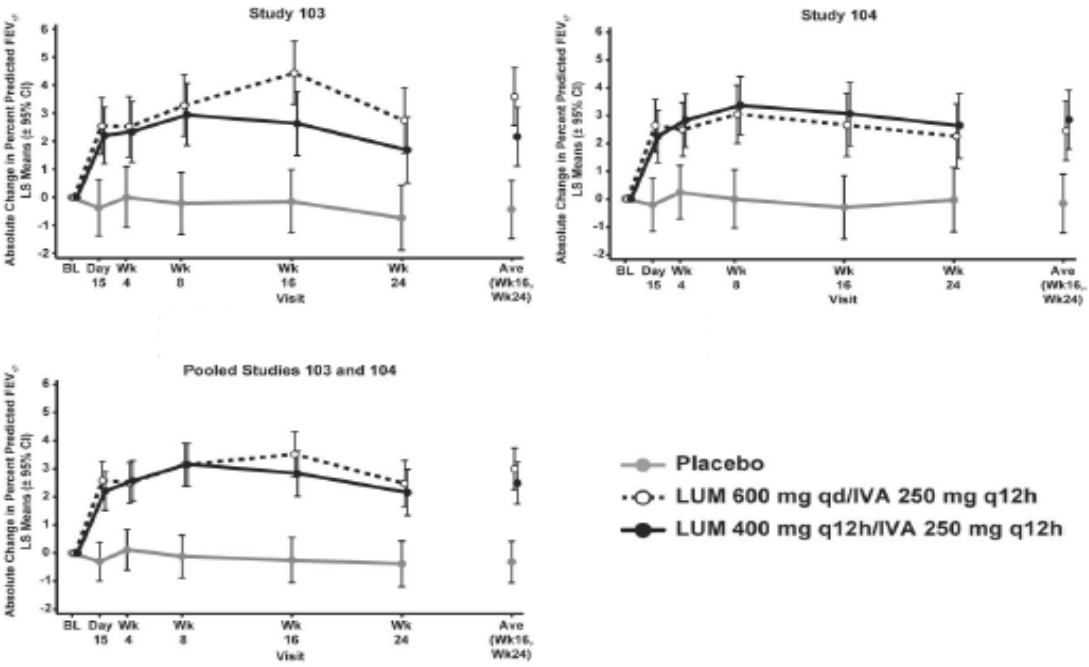
Studies 103 and 104: Absolute change From Baseline in FEV1 (in Liters) at week 24, Full Analysis Set

Statistic	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg q12h/ IVA 250 mg q12h
Study 103	**N = 184**	**N = 183**	**N = 182**
Within-group change (SE)	0.006 (0.0214) *P* = 0.7898	0.121 (0.0214) *P*<0.0001	0.085 (0.0217) *P* = 0.0001
Treatment difference (95% CI)	NA	0.116 (0.058, 0.174) *P* = 0.0001	0.079 (0.021, 0.137) *P* = 0.0081
Study 104	**N = 187**	**N = 185**	**N = 187**
Within-group change (SE)	0.011 (0.0212) *P* = 0.6127	0.105 (0.0212) *P*<0.0001	0.119 (0.0213) *P*<0.0001
Treatment difference (95% CI)	NA	0.094 (0.037, 0.151) *P* = 0.0012	0.108 (0.051, 0.165) *P* = 0.0002
Pooled Studies 103 and 104	**N = 371**	**N = 368**	**N = 369**
Within-group change (SE)	0.008 (0.0150) *P* = 0.6033	0.113 (0.0151) *P*<0.0001	0.102 (0.0152) *P*<0.0001
Treatment difference (95% CI)	NA	0.105 (0.064, 0.146) *P*<0.0001	0.094 (0.053, 0.135) *P*<0.0001

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; NA: not applicable; q12h: every 12 hours; qd: daily; SE: standard error.
Note: N represents the number of subjects in the FAS.

In both, the individual studies and the pooled analysis, improvements in absolute change in percent predicted FEV1 were rapid in onset as shown in the figure below. Significant treatment differences in the absolute change from baseline in percent predicted FEV1 were detected for both dosing regimens by Day 15 (the first post-baseline time point assessment; P≤0.0003) and were sustained at each subsequent visit.

Studies 103 and 104: Absolute Change From Baseline in Present Predicted EFV1 at Each Visit, Full Analysis Set

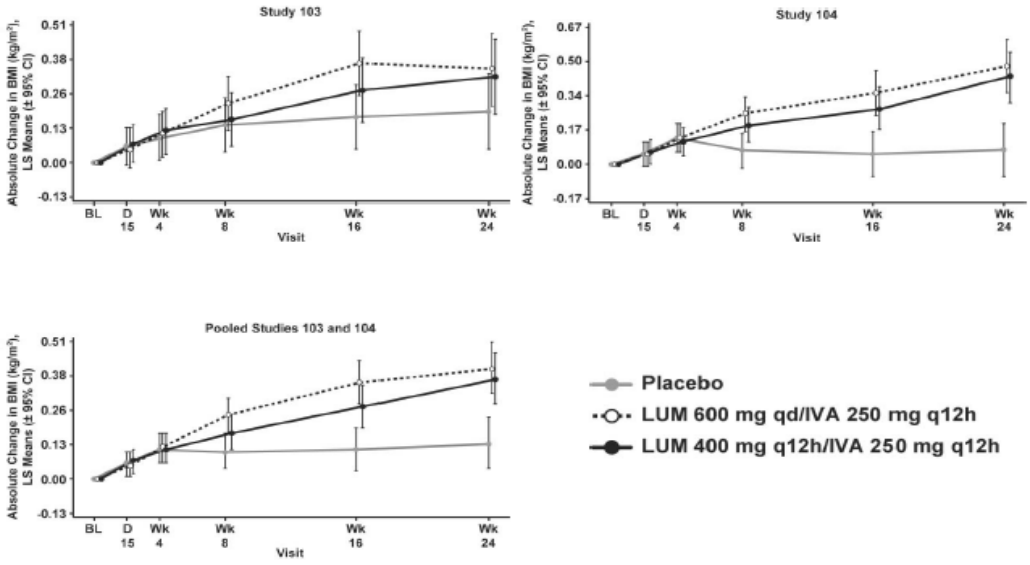


Sources: Module 5.3.5.1/VX12-809-103/Figure 14.2.1.1.1; Module 5.3.5.1/VX12-809-104/Figure 14.2.1.1.1; and Module 5.3.5.3/VX-809 ISE/Figure 3.2.1.1.
Ave: average; BL: baseline; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

The number of pulmonary exacerbations through Week 24 was a key secondary endpoint. In both studies, treatment with lumacaftor in combination with ivacaftor substantially decreased the number, duration, and risk of pulmonary exacerbations, including severe pulmonary exacerbations requiring hospitalizations or IV antibiotic therapy. Time-to-first pulmonary exacerbation through Week 24 and the event of having at least 1 pulmonary exacerbation through Week 24 was a secondary endpoint which is a clinically relevant endpoint. In both Studies 103 and 104, the risk of a pulmonary exacerbation was lower in both active treatment groups compared to the placebo group, and favoured the LUM 400 mg q12h/IVA 250 mg q12h group in both studies.

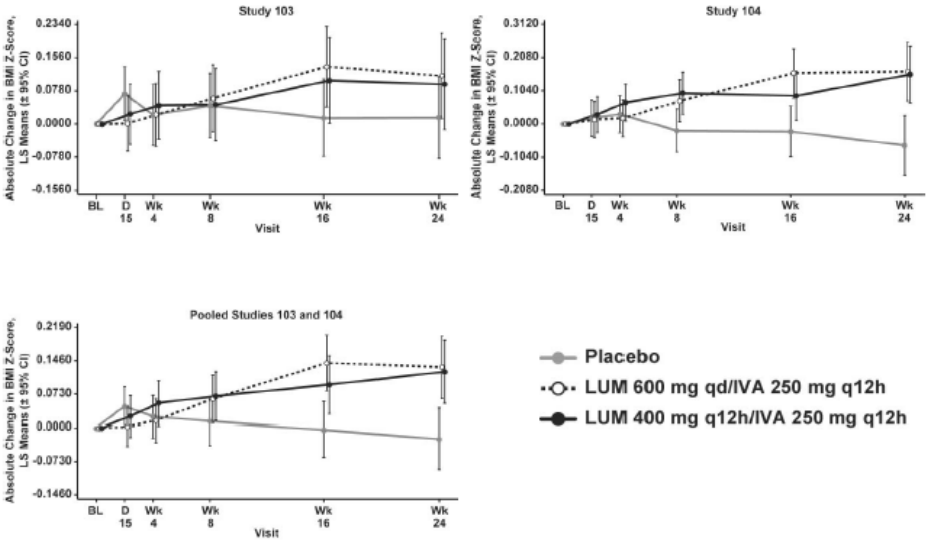
The following figures depict the change from baseline in BMI and BMI Z-score in the individual studies and the pooled data. Of note, the clinical relevance of the increase in BMI has not been discussed taking into account what is known about the correlation between BMI and FEV1.

BMI score: Studies 103 and 104: Absolute Change From Baseline in BMI at Each Visit, Full Analysis Set



Source: Module 5.3.5.1/VX12-809-103/Figure 14.2.2.1, Module 5.3.5.1/VX12-809-104/Figure 14.2.2.1, and Module 5.3.5.3/VX-809 ISE/Figure 3.3.1.1.
BL: baseline; BMI: body mass index; CI: confidence interval; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

Figure: Studies 103 and 104: Absolute Change From Baseline in BMI Z-Score at Each Visit for Subjects Less than 20 Years of Age, Full Analysis Set



Sources: Module 5.3.5.1/VX12-809-103/Figure 14.2.2.2, Module 5.3.5.1/VX12-809-104/Figure 14.2.2.2, and Module 5.3.5.3/VX-809 ISE/Figure 3.3.1.2.
BL: baseline; BMI: body mass index; CI: confidence interval; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; q12h: every 12 hours; qd: daily.

Although there were larger improvements in BMI in the treatment arms as compared to the placebo, the clinical relevance of the noted increase in BMI changes in terms of lung function and overall patient benefit remains largely unknown.

Summary of main studies

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

Table. Summary of efficacy for trial 103

Study VX12-809-103				
Study identifier	Study VX12-809-103 EudraCT Number:2012-003989-40			
Design	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of orally administered Lumacaftor in combination With Ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation			
	Screening Period:		28 days	
	Treatment Period:		24 weeks ± 5 days	
	Safety Follow-up Visit:		4 weeks ± 7 days	
Hypothesis	Superiority			
Treatments groups	LUM 600 mg qd/IVA 250 mg q12h		185 randomized	
	LUM 400 mg q12h/IVA 250 mg q12h		187 randomized	
	Placebo		187 randomized	
Endpoints and definitions	Primary endpoint	Absolute $ppFEV_1$%	absolute change from baseline in $ppFEV_1$ compared to placebo at Week 24, as assessed by the average change at Week 16 and Week 24	
	Secondary endpoint ranked	1.Relative $ppFEV_1$%	relative change from baseline in percent predicted FEV1 at Week 24, assessed as the average treatment effect at Week 16 and at Week 24	
	Secondary endpoint	2.BMI	absolute change from baseline in body mass index (BMI) at Week 24	
	Secondary endpoint	3. CFQ-R	absolute change from baseline in CFQ-R respiratory domain score at Week 24 (for the pooled “Adolescents and Adults” and “Children Ages 12 and 13” versions)	
	Secondary endpoint	4. Response	response defined as ≥5% increase in average relative change from baseline in percent predicted FEV1 at Week 16 and at Week 24	
	Secondary endpoint	5.pulmonary exacerbations	number of pulmonary exacerbations through Week 24	
Database lock	29 April 2014			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	**Full Analysis Set (FAS)** defined as all randomized subjects who received any amount of study drug. The treatment assignment for the FAS was as randomized. The FAS was used for all efficacy analyses			
Descriptive statistics and estimate variability	Treatment group	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h
	Number of subject	184	184	182
	Absolute $ppFEV_1$%	-0.44 (0.524)	3.59 (0.525)	2.16 (0.530)

	Within-group change (SE)	P = 0.4002	P<0.0001	P<0.0001
	Relative ppFEV$_1$%	-0.34 (0.913)	6.39 (0.914)	3.99 (0.923)
	Within-group change (SE)	P = 0.7113	P<0.0001	P<0.0001
	BMI	0.19 (0.070)	0.35 (0.070)	0.32 (0.071)
	Within-group change (SE)	P = 0.0065	P<0.0001	P<0.0001
	CFQ-R	1.10 (1.161)	4.98 (1.178)	2.60 (1.192)
	Within-group change (SE)	P = 0.3423	P<0.0001	P = 0.0295
	Response ≥5%	41	85	67
	Yes, n(%)	(22.3)	(46.4)	(36.8)
	Pulmonary exacerbations	112	79	73
	Number of events (event rate per year)	(1.07)	(0.77)	(0.71)
Effect estimate per comparison	Primary endpoint	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg qd/ IVA 250 mg q12h
		Absolute ppFEV$_1$%	4.03	2.60
		95% CI	(2.62, 5.44)	(1.18, 4.01)
		P-value	P<0.0001	P=0.0003
	Secondary endpoint	**Relative ppFEV$_1$%**	6.73	4.33
		95% CI	(4.27, 9.19)	(1.86, 6.80)
		P-value	P<0.0001	P = 0.0006
	Secondary endpoint	**BMI**	0.16	0.13
		95% CI	(-0.04, 0.35)	(-0.07, 0.32)
		P-value	P = 0.1122	P = 0.1938
	Secondary endpoint	**CFQ-R**	3.88	1.50
		95% CI	(0.70, 7.05)	(-1.69,4.69)
		P-value	P = 0.0168a	P = 0.3569
	Secondary endpoint	**Response ≥5%**	2.9378	2.0592
		95% CI odd ratio	(1.8786, 4.5941)	(1.2920, 3.2819)
		P-value	P<0.0001a	P = 0.0023a
	Secondary endpoint	**pulmonary exacerbations**	0.7186	0.6643
		95% CI (rate ratio)	(0.5170, 0.9987)	(0.4749, 0.9291)
		P-value	P = 0.0491	P = 0.0169a
Notes	The Change from baseline of Predicted FEV1 at Week 24 has been calculated using the Average of Week 16 and Week 24. This choice is not shared either from a regulatory point of view or from a statistical prospective. The Applicant declared that the statistical rationale for the change was to "reduce variability compared with point estimate at week 24 alone". This rational is not supported because the chosen primary analysis method (MMRM) takes itself into account the variability trough the structure of the covariance matrix, and it is not considered appropriate to reduce it by time point averaging.			

Analysis description	The primary analysis for this endpoint was based on a mixed-effects model for repeated measures (MMRM). The model included absolute change from baseline in ppFEV1 as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, age group at baseline, and ppFEV1 severity at Screening, and subject as a random effect. No imputation on missing data was done for the primary analysis using the MMRM. Response, defined as ⩾3, ⩾5, and ⩾10 percentage point increases in average absolute change from baseline in ppFEV1 at Week 16 and at Week 24, was analysed using a 2-sided Cochran-Mantel-Haenszel test. The primary analysis for the first 3 key secondary endpoints was similar to the analysis for the primary efficacy endpoint. Response analyses, similar to those defined for the response of the absolute change from baseline in ppFEV1, were performed for the response defined as ⩾5% increase in average relative change from baseline in ppFEV1 at Week 16 and at Week 24. Regression analysis for a negative binomial distribution, with sex, age group at baseline, and ppFEV1 severity at Screening as covariates and the log of time spent in the study as the offset, was used for the treatment comparison for the number of pulmonary exacerbations.

Table: Summary of efficacy for trial VX12-809-104

Study VX12-809-104			
Study identifier	Study VX12-809-104 EudraCT Number:2012-003990-24		
Design	Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of orally administered Lumacaftor in combination With Ivacaftor in subjects aged 12 years and older with cystic fibrosis, homozygous for the F508del-CFTR mutation		
	Screening Period:		28 days
	Treatment Period:		24 weeks ± 5 days
	Safety Follow-up Visit:		4 weeks ± 7 days
Hypothesis	Superiority		
Treatments groups	LUM 600 mg qd/IVA 250 mg q12h		185 randomized
	LUM 400 mg q12h/IVA 250 mg q12h		187 randomized
	Placebo		187 randomized
Endpoints and definitions	Primary endpoint	Absolute $ppFEV_1$%	absolute change from baseline in $ppFEV_1$ compared to placebo at Week 24, as assessed by the average change at Week 16 and Week 24
	Secondary endpoint ranked	1.Relative $ppFEV_1$%	relative change from baseline in percent predicted FEV1 at Week 24, assessed as the average treatment effect at Week 16 and at Week 24
	Secondary endpoint	2.BMI	absolute change from baseline in body mass index (BMI) at Week 24
	Secondary endpoint	3. CFQ-R	absolute change from baseline in CFQ-R respiratory domain score at Week 24 (for the pooled “Adolescents and Adults” and “Children Ages 12 and 13” versions)
	Secondary endpoint	4. Response	response defined as ≥5% increase in average relative change from baseline in percent predicted FEV1 at Week 16 and at Week 24
	Secondary endpoint	5.pulmonary exacerbations	number of pulmonary exacerbations through Week 24
Database lock	25 April 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		

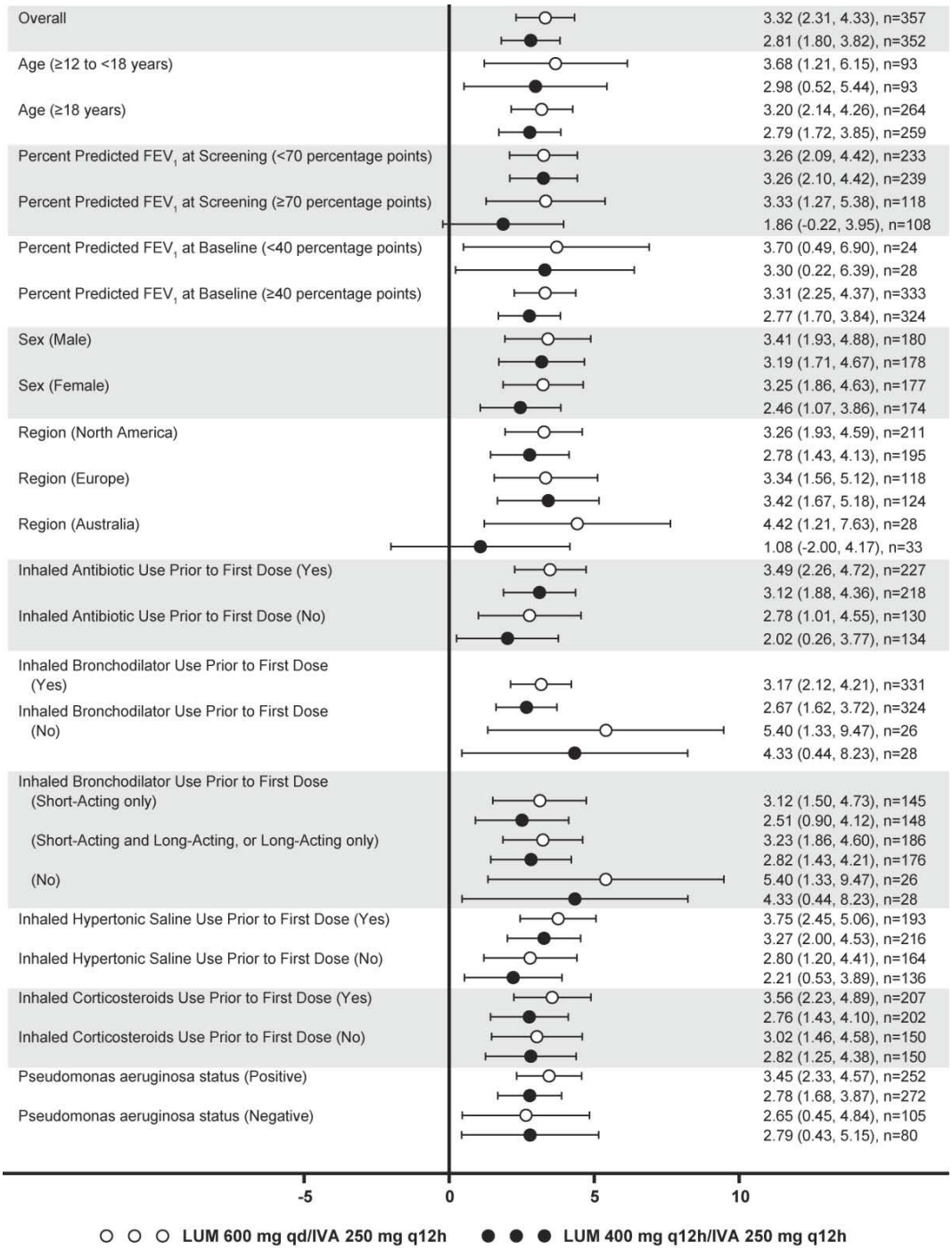
Analysis population and time point description	**Full Analysis Set (FAS)** defined as all randomized subjects who received any amount of study drug. The treatment assignment for the FAS was as randomized. The FAS was used for all efficacy analyses			
Descriptive statistics and estimate variability	Treatment group	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg q12h/IVA 250 mg q12h
	Number of subject	187	185	187
	Absolute ppFEV$_1$%	-0.15 (0.539)	2.46 (0.540)	2.85 (0.540)
	Within-group change (SE)	P = 0.7744	P<0.0001	P<0.0001
	Relative ppFEV$_1$%	0.00 (0.960)	4.42 (0.961)	5.25 (0.961)
	Within-group change (SE)	P = 0.9983	P<0.0001	P<0.0001
	BMI	0.07 (0.060)	0.48 (0.066)	0.43 (0.066)
	Within-group change (SE)	P = 0.2892	P<0.0001	P<0.0001
	CFQ-R	2.81 (1.153)	5.02 (1.166)	5.66 (1.169)
	Within-group change (SE)	P = 0.0152	P<0.0001	P < 0.0295
	Response ≥5%	42	85	77
	Yes, n(%)	(22.5)	(45.9)	(41.2)
	Pulmonary exacerbations	139	94	79
	Number of events (event rate per year)	(1.18)	(0.82)	(0.67)
Effect estimate per comparison	Primary endpoint	Placebo	LUM 600 mg qd/ IVA 250 mg q12h	LUM 400 mg qd/ IVA 250 mg q12h
		Absolute ppFEV$_1$%	2.62	3.00
		95% CI	(1.18, 4.06)	(1.56, 4.44)
		P-value	P=0.0004	P<0.0001
	Secondary endpoint	**Relative ppFEV$_1$%**	4.42	5.25
		95% CI	(1.86, 6.98)	(2.69, 7.81)
		P-value	P=0.0007	P < 0.0001
	Secondary endpoint	**BMI**	0.41	0.36
		95% CI	(0.23, 0.59)	(0.17, 0.54)
		P-value	P < 0.0001	P = 0.0001
	Secondary endpoint	**CFQ-R**	2.21	2.85
		95% CI	(-0.91, 5.53)	(-0.27,5.98)
		P-value	P = 0.1651	P = 0.0736
	Secondary endpoint	**Response ≥5%**	2.9568	2.3834
		95% CI odd ratio	(1.8829, 4.6431)	(1.5234, 3.7286)
		P-value	P<0.0001	P = 0.0001
	Secondary endpoint	**Pulmonary exacerbations**	0.6912	0.5659

		95% CI (rate ratio)	(0.5187, 0.9209)	(0.4191, 0.7641)
		P-value	P = 0.0116	P = 0.0002
Notes	The Change from baseline of Predicted FEV1 at Week 24 has been calculated using the Average of Week 16 and Week 24. This choice is not shared either from a regulatory point of view or from a statistical prospective. The Applicant declared that the statistical rationale for the change was to "reduce variability compared with point estimate at week 24 alone". This rational is not supported because the chosen primary analysis method (MMRM) takes itself into account the variability trough the structure of the covariance matrix, and it is not considered appropriate to reduce it by time point averaging.			
Analysis description	The primary analysis for this endpoint was based on a mixed-effects model for repeated measures (MMRM). The model included absolute change from baseline in ppFEV1 as the dependent variable, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustment for sex, age group at baseline, and ppFEV1 severity at Screening, and subject as a random effect. No imputation on missing data was done for the primary analysis using the MMRM. Response, defined as ⩾3, ⩾5, and ⩾10 percentage point increases in average absolute change from baseline in ppFEV1 at Week 16 and at Week 24, was analysed using a 2-sided Cochran-Mantel-Haenszel test. The primary analysis for the first 3 key secondary endpoints was similar to the analysis for the primary efficacy endpoint. Response analyses, similar to those defined for the response of the absolute change from baseline in ppFEV1, were performed for the response defined as ⩾5% increase in average relative change from baseline in ppFEV1 at Week 16 and at Week 24. Regression analysis for a negative binomial distribution, with sex, age group at baseline, and ppFEV1 severity at Screening as covariates and the log of time spent in the study as the offset, was used for the treatment comparison for the number of pulmonary exacerbations.			

Clinical studies in special populations

This dossier is supported by two pivotal studies (103 and 104) which recruited a similar patient population of CF patients aged 12 years and above who are homozygous with F508del -CFTR. No additional studies in sub-group of patients have been conducted. However, the applicant has conducted a sub-group analysis of the results from the pivotal studies to compare the extent of effects in different sub-groups. The results of the primary endpoint and other endpoints were generally consistent in the different sub-groups. An analysis based on age, sex, baseline disease severity and prior medication use did not show any significant treatment-by-subpopulation interaction. The overall results of the study were not driven by a pre-dominant response in any of the analysed sub-groups. This is reassuring and indicates the results of the studies are equally applicable to all the sub-groups in the population (see table below).

Pooled Studies 103 and 104: Treatment Difference Versus Placebo in Average Absolute Change from Baseline in Percent Predicted FEV1 at Week 16 and at Week 24 by Subpopulations, Full Analysis Set



CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; q12h: every 12 hours; qd: daily. Note: Treatment differences (95% CI), and the number of subjects in the subpopulation are presented

Efficacy in adolescent subjects 12 to 17 years of age

In the 2 pivotal studies 103 and 104, 290 CF adolescent were included. Efficacy results in this patient population mirrored results obtained in adults. In the supportive study 011, examining the efficacy and safety of in subjects 6 through 11 years of age, an abrupt decline in ppFEV1 in 9 of 10 subjects was observed 4 hours post-dose. Overall, the mean ppFEV1 returned to near baseline by day 7 and was

approximately 3 percentage points above baseline at the Safety Follow-up Visit. A similar pattern was observed for ppFVC and ppFEF25%-75%. This drug-induced decrease in ppFEV1 was not expected as no evidence of such an effect was derived from the adult population of CF patients treated with the combination therapy. The mechanism underlying this effect will be investigated by the applicant in the future.

Subjects with ppFEV1 less than 40

Subjects with ppFEV1 less than 40 at screening were in general excluded from both studies. However, a total of 81 subjects (35 subjects in Study 103 and 46 subjects in Study 104) had a ppFEV1 less than 40 at baseline. The majority of these subjects completed treatment. Within this subpopulation, there was a higher percentage of females in both active treatment groups than in the placebo group. Mean baseline BMI and ppFEV1 were similar across all 3 treatment groups. There were some differences between treatment groups with respect to prior use of some CF-related medications; however, these were not significant. Subjects with baseline ppFEV1 less than 40 had absolute improvements in ppFEV1 that ranged from 3.30 to 3.70 percentage points which were comparable to the improvements observed in subjects with baseline percent predicted FEV1 of 40 or greater. Consistent with the improvements in ppFEV1, reductions in the number of pulmonary exacerbations and increases in BMI were also observed in subjects with baseline ppFEV1 less than 40 who received active treatment than in those who received placebo.

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

The results of the analyses of the pooled data from both the pivotal studies (103 and 104) have been presented above under the summary of main efficacy results. The applicant provided the results of studies 103 and 104 based on baseline severity of lung function. These results are presented in the table below.

Subgroup Analyses for Baseline $ppFEV_1$ in Studies 103/104 (Full Analysis Set)

Statistic	Placebo N = 371	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Absolute change from baseline in $ppFEV_1$ at Week 24[a]			
Baseline $ppFEV_1$ (>75)			
n	55	69	58
LS mean difference (95% CI)	NA	1.90 (-1.23, 5.04)	1.43 (-1.82, 4.69)
P value versus placebo	NA	0.2324	0.3863
Baseline $ppFEV_1$ (≤75)			
n	295	277	281
LS mean difference (95% CI)	NA	3.23 (2.06, 4.40)	2.82 (1.66, 3.98)
P value versus placebo	NA	<0.0001	<0.0001
Baseline $ppFEV_1$ (>85)			
n	10	10	8
LS mean difference (95% CI)	NA	-3.65 (-12.27, 4.98)	0.37 (-8.63, 9.38)
P value versus placebo	NA	0.3917	0.9325
Baseline $ppFEV_1$ (≤85)			
n	340	336	331
LS mean difference (95% CI)	NA	3.04 (1.91, 4.17)	2.64 (1.51, 3.77)
P value versus placebo	NA	<0.0001	<0.0001
Absolute change from baseline in BMI at Week 24[a]			
Baseline $ppFEV_1$ (>75)			
n	57	73	62
LS mean difference (95% CI)	NA	0.18 (-0.14, 0.50)	0.15 (-0.18, 0.48)
P value versus placebo	NA	0.2745	0.3703
Baseline $ppFEV_1$ (≤75)			
n	305	283	290
LS mean difference (95% CI)	NA	0.29 (0.15, 0.44)	0.25 (0.10, 0.40)
P value versus placebo	NA	0.0001	0.0009
Baseline $ppFEV_1$ (>85)			
n	10	10	10
LS mean difference (95% CI)	NA	0.65 (-0.17, 1.47)	0.64 (-0.18, 1.47)
P value versus placebo	NA	0.1152	0.1217

A significant proportion of subjects had a baseline lung function ppFEV1 of < 75% and therefore, both the subgroups of >75% and >85% have smaller sample sizes. This is along the expected lines in that patients with CFTR-508del have severe disease. Nevertheless, it is seen that generally the direction of the parameters in primary and secondary endpoints support a treatment effect. A cross- study analysis shows that the treatment effects are consistent across both studies. For the proposed dose of lum 400mg bd/iva 250mg bd, the effects on the primary endpoint was better in study 104 as compared to study 103, but nevertheless, in both studies, a statistically significant superiority over placebo was demonstrated on the primary endpoint. The effects of the proposed dose on exacerbations were better in study 104 as compared to study 103, although both studies showed a clear superiority over placebo. The results on parameters of gastro-intestinal disease/nutrition (weight and BMI) were statistically significant in study 104, whereas the results were numerically superior in study 103.

Regarding the clinical endpoints of pulmonary exacerbations, both studies showed a significant/at least a numerically superior effect in favour of the active treatments. This was seen in all related endpoints. The analysis of the pooled results therefore consistently favours active treatments over placebo on all the primary and secondary endpoints. Thus, the two pivotal studies provide replicating evidence of efficacy for the combination of lum/iva.

It is also noted that the overall treatment effect size on the primary endpoint is small. A substantial proportion of patients (>50%) in both the studies and with both dose-regimens had a less than 5% improvement in ppFEV1. Given that the treatment effects on FEV1 are seen as early as 15 days within

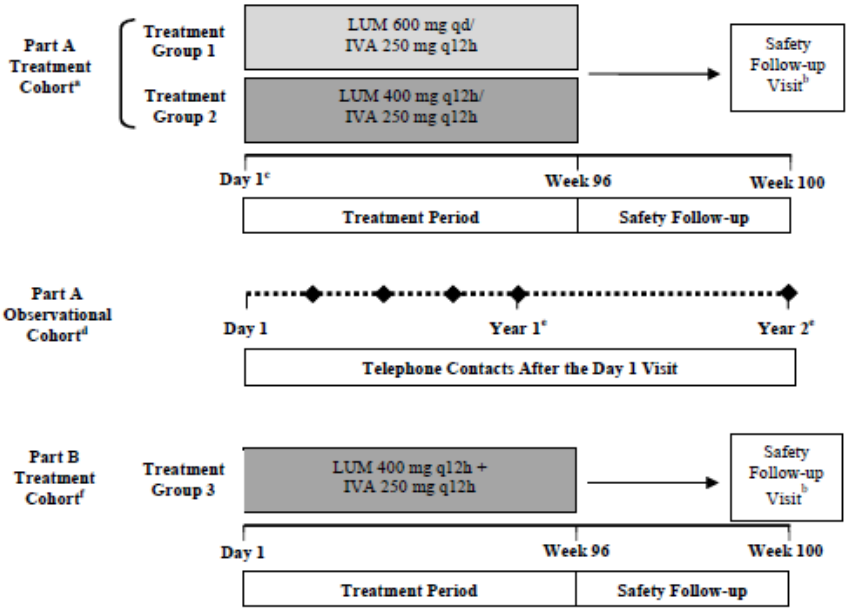
treatment, the applicant was requested to discuss the possibility of identifying non-responders early and develop robust treatment stopping criteria to prevent unnecessarily treating patients who may not get sufficient benefit. In response, the applicant asserts that the observed results on FEV1 are distributed across all sub-groups irrespective of the baseline lung function. Furthermore, the applicant asserts that sub-group analyses have showed that patients had benefits on exacerbations even when there were no observed effects on lung function, based on the results of the below sub-group analyses. Indeed, compared to placebo, LUM/IVA combination therapy substantially decreased the number of pulmonary exacerbations, including severe pulmonary exacerbations requiring hospitalizations and/or IV antibiotics, regardless of whether there was an improvement in ppFEV1 at Day 15. Based on the above analyses, it is agreed that it is not appropriate to select non-responders based on early effects on lung function.

The consistent numerical advantage for the LUM/IVA 400/250mg BD dose-regimen as compared to the LUM 600mg OD/IVA 250mg BD on pulmonary exacerbations across studies 103, 104 and 105 is also acknowledged. There were no specific safety concerns in the LUM/IVA 400/250 mg BD dose-regimen as compared to the LUM 600mg OD/IVA 250mg BD regimen. From a safety perspective, only the off-target broncho-constriction effect of lumacaftor may be amenable to dose-titration. However, there is no clinical data to support such dose-titration and in any case, this safety event was not significant to result in any substantial discontinuations even at the LUM 400mg bd dose-level. Therefore the proposed BD dose regimen which is also convenient, can be accepted based on the currently available data.

Supportive study

Study VX12-809-105 (105) is an ongoing Phase 3, parallel-group, multicenter, 2-part, rollover study in subjects with CF who are homozygous or heterozygous for the F508del-CFTR mutation and who participated in Study 103, Study 104, or Cohort 4 of Study 102. Study 105 is designed to evaluate the safety and efficacy of long-term treatment of lumacaftor in combination with ivacaftor. The schematic design of the study is presented in the figure below.

Schematic of the Study Design



Study 105 Part A, which includes a Treatment Cohort and an Observational Cohort, enrolled subjects who participated in Studies 103 and 104. Study 105 Part B, which includes only a Treatment Cohort, enrolled subjects from Study 102 Cohort 4.

- Part A Treatment Cohort: Subjects from study 103 or 104 who received active treatment in the parent studies continued to receive the same dose-regimen in study 105. Subjects who received placebo in the parent studies were randomized 1:1 to either lum 600mg od/iva 250mg bd or lum 400mg bd/iva 250mg bd
- Part A Observational Cohort: Subjects who met the study criteria for study 105 and who received at least 4 weeks of study drug in Study 103 or Study 104 and who either were not eligible for the Part A Treatment Cohort or chose not to continue treatment with lumacaftor in combination with ivacaftor were eligible for the Part A Observational Cohort. Subjects in the Part A Observational Cohort did not receive study drug.
- Part B Treatment Cohort: subjects who were receiving study drug treatment at the end of treatment in Cohort 4 of Study 102 were enrolled in to the cohort and received lum 400mg bd/iva 250mg bd.

A planned interim safety analysis was performed after 194 subjects who had received active drug in Studies 103 and 104 completed the Week 24 Visit in Study 105; ad hoc efficacy analyses were also performed at the time of this planned interim analysis. The results on ppFEV1 in study 105 are shown in the table and figure below.

Study 105: Absolute Change From Baseline in Present Predicted FEV1 at Each Visit, Part A Cumulative Period, Full Analysis Set

Statistic	LUM 600 mg qd/ IVA 250 mg q12h N = 333	LUM 400 mg q12h/ IVA 250 mg q12h N = 340	Placebo N = 354	Placebo/ LUM 600 mg qd/ IVA 250 mg q12h N = 178	Placebo/ LUM 400 mg q12h/ IVA 250 mg q12h N = 176
Studies 103 and 104 baseline					
n	330	334	347	NA	NA
Mean (SD)	60.92 (13.694)	60.43 (14.236)	60.21 (13.750)	NA	NA
Absolute change at Week 24 of Studies 103 and 104 [a]					
n	315	323	332	NA	NA
Within-group change (SE)	2.73 (0.437)	2.26 (0.435)	-0.39 (0.429)	NA	NA
P value	<0.0001	<0.0001	0.3634	NA	NA
Study 105 baseline					
n	NA	NA	NA	177	174
Mean (SD)	NA	NA	NA	59.21 (14.245)	60.15 (14.779)
Absolute change at Day 15 of Study 105 [b]					
n	319	317	NA	173	165
Within-group change (SE)	2.97 (0.428)	2.77 (0.430)	NA	2.76 (0.575)	2.98 (0.586)
P value	<0.0001	<0.0001	NA	<0.0001	<0.0001
Absolute change at Week 8 of Study 105 [b]					
n	308	316	NA	162	164
Within-group change (SE)	3.07 (0.451)	3.34 (0.448)	NA	2.84 (0.611)	4.12 (0.613)
P value	<0.0001	<0.0001	NA	<0.0001	<0.0001
Absolute change at Week 16 of Study 105 [b]					
n	291	283	NA	152	148
Within-group change (SE)	2.39 (0.488)	2.34 (0.491)	NA	2.59 (0.664)	3.73 (0.672)
P value	<0.0001	<0.0001	NA	0.0001	<0.0001
Absolute change at Week 24 of Study 105 [b]					
n	95	88	NA	45	48
Within-group change (SE)	3.25 (0.672)	2.62 (0.691)	NA	0.47 (0.955)	3.54 (0.937)
P value	<0.0001	0.0002	NA	0.6232	0.0002

Source: Module 5.3.5.2/VX12-809-105 IA1/Ad hoc Table 4.4.2.1a2.

FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; MMRM: mixed-effects model for repeated measures; NA: not applicable; q12h: every 12 hours; qd: daily; SD: standard deviation; SE: standard error.

[a] Three treatment groups were included in the MMRM model. Baseline was defined as the last non-missing measurement before the first dose of study drug in Study 103 or 104.

[b] Four treatment groups were included in the MMRM model. Baseline was defined as the last non-missing measurement before the first dose of active study drug. For the LUM 600 mg qd/IVA 250 mg q12h group and the LUM 400 mg q12h/IVA 250 mg q12h group, baseline values from Studies 103 and 104 were used. For the placebo/LUM 600 mg qd/IVA 250 mg q12h group and the placebo/LUM 400 mg q12h/ IVA 250 mg q12h group, baseline values from Study 105 were used.

The interim analysis from study 105 provides evidence on long-term maintenance of efficacy and safety; i.e. treatment effects after 48 weeks of treatment with the combination, where for the first 24 weeks there is parallel placebo treatment group for comparison and for the second 24 weeks it is uncontrolled. In subjects who were on placebo in the previous study and then randomized to active treatment in this study, it was seen that patients had treatment benefit within 15 days of starting treatment and this was generally maintained up to week 24 of treatment in the lum 400mg bd/iva 250mg bd. The extent of benefit in the treatment groups who were initially on placebo in the parent studies seems broadly

comparable to the benefit obtained by patients who started active treatment in the parent studies. This provides further evidence of the efficacy of the combination.

Second Interim analysis of study 105

A planned interim analysis was performed after all subjects in the Part A Treatment Cohort (Studies 103 and 104) completed the Week 24 Visit in Study 105 and all subjects in the Part B Treatment Cohort (Cohort 4 of Study 102) completed the Week 16 Visit in Study 105. Efficacy analysis in Part A included 1029 subjects in the full analysis set. Data for 48 weeks of treatment with LUM/IVA combination therapy were available for 629 subjects who were assigned to 24 weeks of active treatment in Studies 103 or 104 followed by 24 weeks of active treatment in Study 105. The rapid and sustained improvements in percent predicted forced expiratory volume in 1 second (ppFEV1) observed in the groups treated with LUM/IVA combination therapy for 24 weeks in studies 103 and 104 were durable after an additional 24 weeks of LUM/IVA combination therapy in study 105 for a total of 48 weeks of active treatment. The groups treated with LUM/IVA combination therapy for 24 weeks in studies 103 and 104 improved also in BMI, weight, and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain scores that were durable through an additional 24 weeks of active treatment in Study 105. For the groups that received LUM/IVA combination therapy in Studies 103 and 104, the annualized rate of pulmonary exacerbations remained lower in both groups than placebo treatment in the previous studies after an additional 24 weeks of LUM/IVA combination therapy in Study 105. Importantly, the annualized rate of pulmonary exacerbations that required hospitalization and the raw annualized rate of pulmonary exacerbations requiring IV antibiotic therapy remained lower in both groups than placebo treatment in the previous studies. The overall small effect size on lung function has been discussed by the applicant using a model built on the above long-term data. Results show that LUM/IVA decreased the rate of ppFEV1 decline compared with placebo. Given the duration of observation to date, the lack of statistical significance is not unexpected. Although the difference between the LUM/IVA and placebo rates of decline is not yet statistically significant, a treatment effect is clearly evident.

It is noted that the rate of decline in the placebo-treated patient is lower from that observed from registry populations of patients homozygous for F508del. The applicant argued that this could lead to an underestimation of treatment effect. However, differences in the rate of decline may well relate to differences in disease severity and aggressiveness because of the variable presence and combination of risk factors in different patient subpopulations. It is unknown if treatment effect would be similar in patient populations with faster rates of decline in lung function. The applicant provided a sub-group analysis in patients on placebo in study 103/104 and who had a more than 2 percentage points decline in ppFEV1 (n=35) and more than 5 percentage points decline in ppFEV1 (n=7). Although arbitrary, this definition may be considered acceptable even if it does not take into account other parameters indicative of rapidly progressive pulmonary disease related to patient-specific changes, such as the rate of pulmonary exacerbations, intermittent infections or onset of CFRD. Results from this analysis show comparable efficacy of LUM/IVA treatment in the different subgroups of patients, including those with more than 10% annual decline in ppFEV1. However, due to the small number of patients who can be thus defined as rapidly progressive, the inferences drawn are not robust. A reliable evaluation of the activity of LUM/IVA in patients with rapidly progressive pulmonary disease is possible only in the post-marketing setting.

To evaluate the consistency in effects, the applicant was requested to provide a comparison of the exacerbation data for the first 24 weeks (in study 103 and 104) with exacerbation data in second 24 weeks (in study 105) for patients who had started active treatment in study 103/014. This analysis was provided by the applicant as below.

Table 4 **Comparison of Pulmonary Exacerbation Event Rates During First 24 Weeks of Treatment (Studies 103/104) and Second 24 Weeks of Treatment (Study 105) in Patients Treated in Studies 103/104 and Study 105**

First 24 Weeks (Studies 103/104)	LUM600qd/IVA	LUM400q12h/IVA	Placebo	
Number of patients	334	340	355	
Event rate per year, 95% CI	0.82 (0.68, 0.98)	0.67 (0.55, 0.82)	1.12 (0.95, 1.32)	
Second 24 Weeks (Study 105)	**LUM600qd/IVA**	**LUM400q12h/IVA**	**LUM600qd/IVA**	**LUM400q12h/IVA**
Number of patients	334	340	179	176
Event rate per year, 95% CI	0.84 (0.69, 1.02)	0.61 (0.49, 0.75)	0.81 (0.62, 1.04)	0.64 (0.48, 0.85)

Sources: Ad Hoc Table 4.4.13.2.5.2.1a3, Ad Hoc Table 4.4.13.2.5.2.2a3

These results compared to the placebo treatment period showed these patients had a reduced rate of pulmonary exacerbations during LUM/IVA treatment in Study 105, and the event rates during Study 105 were comparable to those of patients treated with 24 weeks of LUM/IVA in Studies 103/104 demonstrating maintenance of effects.

In relation to the query on the potential impact of the imbalances in antibiotic use between the treatment arms on the outcomes, the applicant's response addressed the use of both inhaled and oral antibiotics. It was seen that the use of antibiotics was generally higher in the placebo group as compared to the active treatment arms. This would have probably biased the results against treatment, if at all this had an effect. The applicant was also requested to provide and discuss a cross-study comparison of the observed effects with LUM/IVA as compared to the effects for other treatments currently used in this patient population as evidenced in published literature to provide a comparative perspective of the treatment effect size. Although the comparisons are not robust, it can be seen that the treatment effects of LUM/IVA is comparable to other treatments authorised in cystic fibrosis. Moreover these effects were observed in addition to the effects of standard of care. Hence, this in general supports the clinical relevance of the observed results. However for a disease-modifying therapy, these effects are small and the treatment needs to be taken continuously for life. This can only be justified if there is a meaningful alteration in the disease progression by reducing the slope of deterioration in lung/organ function. In this context, the CHMP considers that data on the maintenance of treatment effect over time (long-term efficacy beyond 1 year) can be provided in the post-authorisation setting. The study 105 is ongoing and the applicant is committed to provide clinical data of 120 weeks of treatment from this study as described in the RMP.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two pivotal studies (study 103 and study 104) have been conducted in support of the use of Orkambi. Both were similar and were randomized, double-blind, placebo controlled studies. CF patients aged 12 years and above who were homozygous for F508del-CFTR were enrolled. The Applicant justified the inclusion of paediatric patients aged 12 years and older in the pivotal studies because they are expected to have similar levels of disease activity as adults, the same clinical end-points are established for both adolescents and adults with CF, and because extrapolation of dose from adults is possible for this age group. This is acceptable in principle, although it is noted that age is a key determinant in the evaluation of disease severity and consequently treatment benefit. As such, the interpretation of efficacy data in adolescents needs to take into account the more complex clinical picture of the disease at this age.

The studies have the same design, including a Screening Period, a Treatment Period of 24 weeks, and a Safety Follow-up of additional 4 weeks, which is in line with the relevant CHMP guideline and is considered in general adequate to the evaluation of treatment effect in the claimed indication. However, both pivotal trials included a very large number of study sites located in North America, Europe and Australia. Thus only a small proportion of potentially eligible patients could have been enrolled at each site, which hypothetically could have introduced bias in enrolment. The subgroup analysis differentiating between US, EU and Australian centres was not considered adequate to the CHMP to reveal potential recruitment bias, and additional subgroup analysis stratified by quartiles of proportions of randomized patients out of screened patients has been requested and it was reassuring the see that the treatment effect in both treatment arms does not seem to be driven by study sites with a low percentage of randomized patients.

The inclusion and exclusion criteria allow the enrolment of a patient population that adequately represents the target patient population of the sought indication. Genotyping was performed using a validated CF genotyping test. Similar to that selected in the Kalydeco dossier, enrolment was limited to subjects with a FEV1> 40 and < 90 percent of predicted normal for age, sex and height at screening. This corresponds to patients with moderate-severe lung disease who on the basis of what is known for ivacaftor are more likely to respond to treatment. Subjects were kept on their prescribed CF therapies for the entire study duration. Therefore, the combination of LUM/IVA was added to the usual patient background regimen. Standardization of concomitant therapy does not seem to have been done. As a consequence, results should be interpreted with caution sharp-cutting the background regimen.

Primary Endpoint

The Guideline on Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis (EMEA/CHMP/EWP/9147/2008-corr*) recommends “at least a 6-month clinical primary endpoint assessing the respiratory function through FEV1 measurement”, and further specifies that “the time-point for the clinical endpoint should allow concluding on the long-term benefit for patients”. The primary endpoint selected for both 103 and 104 studies differs from what is recommended in the guideline because it is assessed by the average change at Week 16 and Week 24, and not, as requested, at week 24. Absolute changes from baseline in ppFEV1 at week 2, 4, 8, 16 and 24 have been included as an additional analysis. For the evaluation of treatment effect absolute changes from baseline in ppFEV1 at week 24 will be considered as the most reliable efficacy data and this has also been reflected in the SmPC of Orkambi.

Crucial for the correct interpretation of the ppFEV1 endpoint is effective standardization of spirometry. At the investigation site, spirometry was performed pre-bronchodilator and before dosing, according to the American Thoracic Society Guidelines. In particular, patients who were on SABA or SAMA, were withdrawn from bronchodilators 4 hours before the spirometry assessment; whereas patients on LABA or LAMA withheld bronchodilator 12 hours or 24 hours before treatment, as appropriate. However, if patients forgot to withhold bronchodilators before spirometry, spirometry was performed post-bronchodilator. The applicant has provided analyses to show that not withholding bronchodilators before spirometry would not significantly affect the conclusions of the study, which is re-assuring.

In addition, evidence from Studies 102, 008 and 009 showed a decline in FEV1 4 hours post-dose. No information is provided for studies 103 and 104, with the exception of 1 adolescent patient who discontinued treatment due to FEV1 decrease. The Applicant clarified that there were no acute assessments on FEV1 immediately after dosing in study 103 and 104. The actual assessments show that there was a beneficial effect of treatment on FEV1 within 15 days of treatment initiation and the number of withdrawals in these long-term studies is small, which suggests that this decline in post-dose FEV1 was not a significant concern. While this is accepted, the applicant took in to consideration that in practice, patients who are in exacerbation/poor and unstable lung function may be initiated on therapy. The SmPC

advises that there is no experience of initiating treatment with lumacaftor/ivacaftor in patients having a pulmonary exacerbation and this is not advisable. This is considered appropriate by the CHMP.

Key secondary endpoints

Five key ranked-secondary endpoints were selected in both pivotal trials and the CHMP considered them important read-outs of treatment effect. From a clinical point of view the most important endpoint is recurrent pulmonary exacerbations which is associated with long-term decline in lung function and shortened survival; BMI is also considered of relevance since it is an index of patient nutritional status that is severely affected in CF. Because lumacaftor in combination with ivacaftor targets the underlying defect in CF, an endpoint that allows to monitor the systemic clinical benefit of the combination therapy is important in order to evaluate treatment benefit. The responder analysis is also considered key for the interpretation of treatment efficacy. Patient perception of treatment-induced clinical benefit was monitored by CFQ-R respiratory domain score, which is a validated tool investigating cough during the day and night, the presence of mucus, and the ease of breathing. A difference of at least 4 points in the CFQ-R respiratory domain score, has been assumed as the minimal clinical important difference (MCID); this is considered acceptable as it is supported by literature evidence. No endpoint directly demonstrating on-target activity of the combination therapy (e.g. measurement of sweat chloride concentration) has been included in the pivotal studies. The applicant justified this exclusion stating that the primary aim of the pivotal trials was the demonstration of a clinically sustained benefit, whereas evaluation of drug effect on target was limited to the phase 2 studies, which included sweat chloride measurements. Measurement of sweat chloride is affected by high intra-patient variability which needs to be taken into account by comparing study results with previous determinations in the same patient.

Two dosing regimens of the combination were evaluated: lum 600mg qd/iva 250mg bd and lum 400mg bd/iva 250 mg bd. This was based on the results of study 102. In both regimens the dosage of lumacaftor was higher than that approved for the monotherapy (i.e. 150 mg q12h) because of the observed reduction in ivacaftor exposure when administered in combination with the CYP3A inducer lumacaftor. Treatment duration was 24 weeks, which is adequate. On the basis of PK data, Orkambi was administered with high-fat, high-calorie meal as the fed state increases the systemic exposure. This is reflected in the SmPC.

The pivotal studies used a placebo comparison and did not include a lumacaftor alone treatment comparison. For the rational use of a fixed dose combination it is necessary to show that the combination is better than the relevant monotherapies. As lumacaftor monotherapy was not fully characterised in phase 2 setting, the lack of monotherapy comparator was an issue. However, in this instance where LUM/IVA is targeted at an orphan indication and where treatment benefit is demonstrated on top of standard of care, the limited data on short term clinically relevant benefit on lung function from phase 2 study is accepted by the CHMP.

The power of the studies, with the selected sample size of 501 patients, is > 99.9%. Indeed less than 60 pts per arm would have sufficed to detect a treatment difference of 5 percentage points in absolute change of percent predicted FEV1 between study arms with a power of 90%. The studies thus have a large sample size. In addition, considering that the final randomized population is larger than planned and consist of 559 and 563 patients in study 103 and 104, respectively, the demonstration of a statistically significant effect is not of much value unless the effect size can be justified to be clinically relevant. When the population of the 2 studies is pooled a total of 1108 pts are analyzed to produce overall efficacy estimates. Clinically irrelevant differences between treatment doses and placebo will thus result as statistical significant, negatively impacting on the interpretation of study results in terms of p values. However this sample size is justified based on the need to adequately characterise the safety profile of the combination.

A mixed-effects model for repeated measures (MMRM) was used as the primary analysis method to determine the treatment effects. A hierarchical testing procedure was used for the primary and key secondary endpoints at α = 0.0250 for each active treatment arm separately. At each step, the test for treatment effect was considered statistically significant if the p value was ≤0.0250, and all previous tests also met this level of significance. For endpoints on ppFEV1, the change from baseline to week 24 was calculated as an average of week 16 and week 24. This is not truly reflective of a treatment effect after 6 months of treatment and so the applicant was requested to provide analysis based on observations at week 24 alone. Hence, as requested by the CHMP, the applicant agreed to present the change at week 24 data for spirometric values in the SmPC.

Overall, the proposed two studies provide replicated evidence on the treatment effects of the combination in the intended target population on clinically relevant parameters after adequate treatment duration. In addition, for further evidence on long-term safety and maintenance of efficacy, the applicant has submitted the results of two interim analyses from an ongoing study (study 105) which enrolled patients who had completed phase 2/phase 3 studies of the combination.

Efficacy data and additional analyses

Both the pivotal studies, study 103 and study 104 were positive and showed statistically significant superiority over placebo on the primary endpoint of mean absolute change from baseline in ppFEV1 at week 24 in both lum 600mg qd/iva 250 mg bd (study 103 – 2.73%, p<0.0001; study 104 – 2.26%, p=0.0001) and lum 400mg bd/iva 250 mg bd (study 103 – 1.68%, p=0.005; study 104 – 2.63%, p<0.0001). Most of the treatment effect was already apparent at day 15, reached a peak at week 16, and slightly decreased at week 24. Treatment effect on the first key secondary endpoint, average relative change from baseline in ppFEV1, was consistent with results observed for the primary endpoint. The effects on secondary endpoints which included surrogate (spirometric), clinical (BMI, exacerbations) and patient reported outcomes (CFQ-R, TMSQ & EQ-5D-3L) were all consistently in favour of the active treatments (both doses) as compared to the placebo in both study 103 and 104 with many of them meeting statistical significance as well. On the clinical endpoints of pulmonary exacerbations, importantly robust reductions in the number, frequency, and duration of pulmonary exacerbations, including severe pulmonary exacerbations requiring hospitalization or IV antibiotic therapy, were also observed following treatment.

At Week 24, in subjects treated at the proposed dose of lum 400mg bd/iva 250mg bd, the proportion of patients who remained free from pulmonary exacerbations was significantly higher as compared to placebo. In the pooled analysis, the rate ratio of exacerbations through Week 24 in subjects treated with lumacaftor 400 mg/ivacaftor 250 mg q12h; n = 369 was 0.61 (P<0.0001), representing a reduction relative to placebo of 39%. Treatment with lumacaftor 400 mg/ivacaftor 250 mg q12h significantly decreased the risk for exacerbations requiring hospitalisation vs. placebo by 61% (rate ratio=0.39, P<0.0001) and reduced exacerbations requiring treatment with intravenous antibiotics by 56% (rate ratio=0.44, P<0.0001). There is additional support from the long-term uncontrolled study (study 105) which shows that the efficacy seen at 24 weeks in study 103 and 104 was maintained up to week 48 in patients who continued on active in both study 103/104 and study 105. Patients on placebo in study 103/104 who then received active treatments in study 105 also showed the same magnitude of benefit providing further evidence for the treatment effect of lum/iva.

In the pivotal studies, the magnitude of treatment effect on the primary endpoint is smaller than the 5% difference on which the sample size calculations were based. Further, the statistical significance appears to be driven by the large sample size rather than a large effect size, and significance per se cannot be the only factor that supports the demonstration of efficacy. The analysis of responders further confirms the limited benefit of the combination therapy with only 30.8%-37% and 23-30% of patients in the two studies treated with the 600 mg LUM qb/IVA and 400 mg LUM q12h/IVA, respectively, showing an

absolute gain in ppFEV1 over baseline of > 5%. Similar results are obtained when response to treatment is defined as >5% relative improvement in ppFEV1. Of note, there was a high rate of responders in the placebo groups, which may impact the interpretability of treatment effect.

In Study 103, treatment effect failed to reach statistical significance over placebo for the second key secondary endpoint: changes in BMI, stopping the testing hierarchy at this endpoint for both active treatment groups. Treatment failure in increasing BMI was accompanied by similar not statistically significant results in absolute change in body weight and in BMI z-score at week 24. The applicant justifies the lack of a statistical significance effect on BMI with the observation that the placebo group showed a significant within-group improvement in BMI (0.19 kg/m2; P = 0.0065). Indeed, the fact that patients treated with placebo had significant increases in BMI indicates that fluctuations in this endpoint may be observed in the clinical course of the disease, challenging the interpretation of study results. In Study 104, both dosing regimens of the combination therapy resulted in statistically significant increases in BMI over placebo. Results on BMI were mirrored by similar treatment effect on body weight at week 24. Analyses of absolute changes in body weight and in BMI z-score at week 24 yielded similar results. However, it is difficult to judge treatment effect on BMI without taking into consideration the changes in the nutritional risk at the single patient level in response to the improvement in BMI.

An absolute difference of 30-40% in the number of pulmonary exacerbations was observed in the active treatment arms compared to placebo in both pivotal trials. These results are not statistically significant based on the hierarchical testing. The analysis of time-to-first pulmonary exacerbation through Week 24 confirmed that a numerically greater proportion of subjects who received the LUM/IVA combination therapy remained free of pulmonary exacerbations compared with the proportion of subjects who received placebo. The rate of severe pulmonary exacerbations requiring hospitalization was also reduced in the active treatment arms compared to placebo. This was paralleled by and a lower number of pulmonary exacerbations requiring IV antibiotic therapy through Week 24. Although not outstanding, these overall results are considered of interest if maintained in the long-term.

In the results of the pivotal studies, subgroup analyses were performed for the primary endpoint, by stratifying for demographic and baseline characteristics and for prior medication subgroups. No robust trends suggestive of meaningful differences between any of the subgroups were seen. Data on absolute ppFEV1 changes over baseline from the rollover study 105 seem to confirm maintenance of treatment effect up to a total of 48 weeks of therapy.

In the first interim analysis, subjects randomized to placebo in studies 103 and 104 and receiving the 600 mg LUM qd/IVA combination therapy showed a fall in response at week 24 of Study 105. The applicant interpreted these data with caution because of the small number of subjects included in the analysis (45 pts treated with placebo/600 mg LUM qd/IVA). Of note, although of similar size, the correspondent treatment arm with the 400 mg LUM q12h/IVA did not show any decrease in treatment effect. In the second interim analysis, it is noted that subjects who were initially on placebo in study 103 and 104 and then rolled over to active treatments showed a beneficial effect on ppFEV1 in both dosing regimens.

Furthermore, the evidence from study 105 suggests that patients who were on placebo in the parent study (103 or 104) achieved a similar magnitude of benefit as patients who had lum/iva through both parent and long-term extension studies. Hence, the treatment effect of the combination lum/iva could provide around 2% benefit on ppFEV1 and may not alter the slope of decline in FEV1. The applicant submitted additional data from second interim analysis of study 105. Although based on extrapolation, the applicant asserts that an effect on the slope of decline in FEV1 has been demonstrated. Another aspect of justifying the need for chronic treatment is the effect on exacerbations, which is of direct clinical relevance; a continued reduction in exacerbations throughout the treatment period was demonstrated, which is beneficial.

Several intervention strategies have been shown to reduce the number of acute exacerbations with comparable efficacy as the LUM/IVA combination therapy. The applicant was asked to discuss the relevance of the potential benefit on the rate of exacerbation of the combination therapy in the context of the available armamentarium for the management of CF. This comparison showed that the treatment effect size of LUM/IVA was comparable to other authorised symptomatic treatments in CF. This is both, reassuring on the clinical relevance of the observed effect size, but questioned in that the effect size of a chronic treatment which targets disease modification is only comparable to other symptomatic treatments. Nevertheless, considering that the observed benefits are in addition to the benefits of standard of care, it is accepted that adequate evidence of clinically relevant and statistically significant effect on efficacy has been demonstrated. Given the overall limited magnitude of beneficial effect seen on the primary endpoint, a longer follow up period is required to provide additional conclusive evidence on the long-term efficacy. Hence, in study 105, the applicant should explore the possibility of a longer (i.e. 5 years) follow up of the enrolled patients and provide results on the agreed efficacy and safety of this study population and report in PSURs as recommended by the CHMP. This will be forthcoming as study 105 is ongoing.

2.5.4. Conclusions on the clinical efficacy

Statistical Conclusions

The results from both studies provide good evidence that both active combination arms are superior to placebo in terms of effects on FEV1 after 24 weeks of treatment. Additional analyses of change from baseline to week 24 using multiple imputation to account for missing data were supportive of the initial conclusions. The primary analysis presented estimates the average of the effect at Week 16 and 24. This estimate is slightly larger than the analysis of the change from baseline to Week 24, which is therefore considered to provide a better estimate of the likely long term efficacy of the combination and the applicant has accepted the recommendation to include these results in the SmPC, as required by the CHMP.

Clinical conclusions

A consistent and statistically significant treatment effect for both the dosing regimens of lumacaftor and ivacaftor combination therapy was shown on the primary endpoint of mean absolute change in ppFEV1 from baseline at week 24. The onset of treatment effects was seen as early as 15 days after start of treatment. This effect was generally maintained for the study treatment period of 24 weeks. Further the long-term extension study showed that efficacy at 24 weeks, which was generally maintained up to 48 weeks.

Consistent support from PD data for the proposed mechanism is not available as the available PD data is limited. The added advantage of IVA in terms of a clinically relevant effect to the combination cannot be conclusively ascertained in the absence of comparison of the combination to lumacaftor monotherapy. However in the context of a disease modifying treatment, in an orphan condition where the benefits is on top of current standard of care, the available short-term data showing the added benefit of ivacaftor on lung function is accepted.

The extent of effect seen (1.68%-2.63%) is lower than anticipated 5% change. This is also lower than the reported 10-12% improvement with the only disease modifying treatment that has been authorised - ivacaftor in G551D patients. This extent of effect is closer to symptomatic treatment. Clinical benefit from an accrued benefit in FEV1 expanding with time from a 2% baseline can be of significance. The rate of decline of FEV1 in the population enrolled in the pivotal studies appears slower than what is documented from registry. Further the number of exacerbations is lower than in a general CF population and the number of patients who are considered to have rapidly progressive disease appears to be small in the

study population. It is accepted that these are limitations that are expected in controlled clinical studies. Because of this limitation, the generalizability of the study results can be conclusively ascertained only in a post-marketing setting.

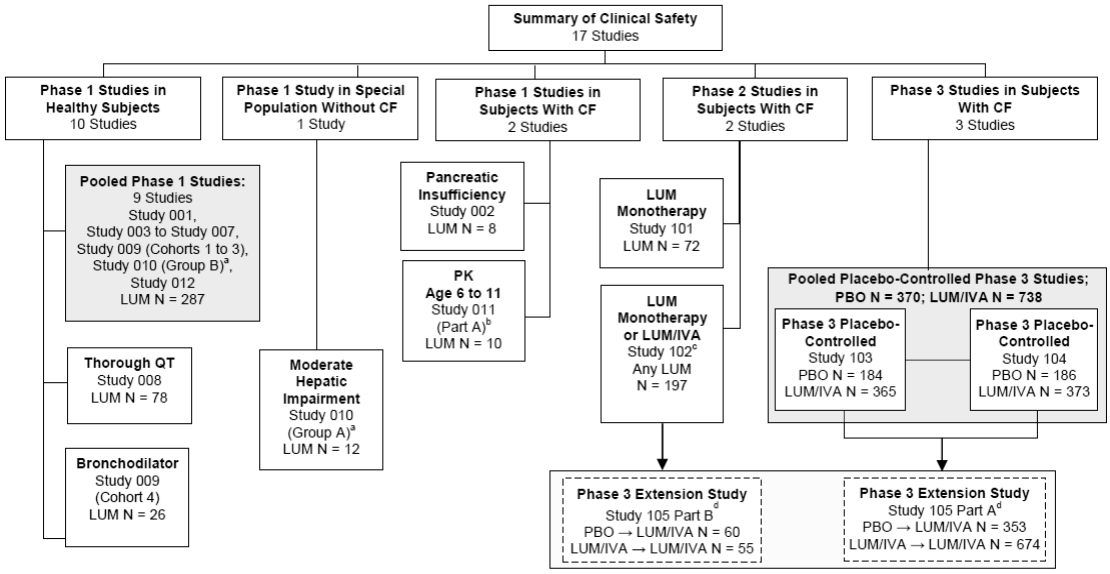
The results on the key secondary endpoints and other secondary endpoints were supportive of the conclusion from the primary endpoint including significant effects on clinical outcome endpoints related to exacerbations. The effects on CFQ-R and BMI have not been consistently significant across the studies and are not in themselves indicative of a clinically relevant benefit of the treatment. An absolute difference of 30-40% in the number of pulmonary exacerbations was observed in the active treatment arms compared to placebo in both pivotal trials which is accepted as clinically meaningful effect. The analysis of time to first pulmonary exacerbation, rate of severe pulmonary exacerbations requiring hospitalization and rate of pulmonary exacerbations requiring IV antibiotic therapy were all supportive of a clinically relevant treatment effect.

Taking the overall evidence, it is concluded that adequate evidence of a significant and clinically relevant effect on efficacy has been demonstrated. Given the low magnitude of observed effect on the primary endpoint further long-term data on the forthcoming from the ongoing study 105 will be submitted as described in the RMP. Furthermore the applicant has been asked to explore the possibility of a longer (i.e. 5 years) follow up of the enrolled patients and provide results on the agreed efficacy and safety of this study population and report in PSURs.

2.6. Clinical safety

The safety analysis includes all safety data available as of 21 July 2014 from 17 clinical studies with lumacaftor monotherapy or lumacaftor in combination with ivacaftor.

Overview of Studies (N=17) and Pooling in the safety data



Sources: Module 5.3.5.3/VX-809 ISS SAP/Section 1.4; Module 5.3.5.3/VX-809 ISS/Tables 1.1.2 and 2.1.7; Module 5.3.3.2/VX07-809-002; Module 5.3.4.1/Study VX12-809-008; Module 5.3.3.4/VX12-809-009; Module 5.3.3.3/VX13-809-010; Module 5.3.3.2/VX13-809-011; Module 5.3.4.2/VX08-809-101; Module 5.3.4.2/VX09-809-102; Module 5.3.5.1/VX12-809-103; Module 5.3.5.1/VX12-809-104; Module 5.3.5.2/VX12-809-105 IA 1.

CF: cystic fibrosis; IVA: ivacaftor; LUM: lumacaftor; N: number of subjects who received at least 1 dose of lumacaftor (any dosage, alone or in combination with ivacaftor); PBO N: number of subjects who received at least 1 dose of placebo; PBO → LUM/IVA N: number of subjects who received placebo in a placebo-controlled study and then received at least 1 dose of lumacaftor in combination with ivacaftor in an uncontrolled extension study; LUM/IVA → LUM/IVA N: number of subjects who received lumacaftor in combination with ivacaftor in a placebo-controlled study and then received at least 1 dose of lumacaftor in combination with ivacaftor in an uncontrolled extension study; PK: pharmacokinetic; SCS: summary of clinical safety

The core safety data are pooled analyses of 2 placebo-controlled Phase III studies of LUM/IVA in subjects with CF who are homozygous for the CFTR-*F508del* mutation. The supportive analysis includes pooled safety data from 9 Phase 1 studies (lumacaftor monotherapy and lumacaftor in combination with

ivacaftor) in healthy subjects. Safety data from 6 individual Phase I and II studies are also included. Of the subjects who received at least 1 dose of LUM/IVA combination therapy in the pooled Phase III studies (103 and 104), 56.6% were in North America, 35.0% were in Europe, and 8.4% were in Australia. The majority of these subjects were White (98.2%), not Hispanic or Latino (96.3%), and 18 years of age or older (73.7%).The proportion of male subjects (50.7%) and female subjects (49.3%) was similar.

The median age was 24 years in the LUM/IVA group and 23 years in the placebo group. Baseline disease characteristics show that the proportion of subjects distributed across the different ranges of percent predicted FEV1 were similar across the LUM/IVA and placebo groups.

Patient exposure

A total of 116 patients who had been exposed to lumacaftor/ivacaftor in the placebo-controlled Phase III studies (103 and 104) had completed the 24-week visit in Study 105 and had therefore been exposed to either dose of lumacaftor/ivacaftor for at least 48 weeks as of 21 July 2014. Hence, more than 100 patients have been exposed to lumacaftor/ivacaftor combination therapy for at least 48 weeks in line with the guidelines on minimum exposure data for safety purposes of long-term therapy.

Patient exposure till 21 July 2014

	Patients enrolled	Patients exposed		Patients exposed to the proposed dose range	Patients with long term* safety data
		Lum	Lum/Iva	(Lum/Iva 400/250 q12h)	(Lum/Iva 400/250 q12h or 600/250 q12h))
Placebo-controlled	1108		738	369	692
Active -controlled		138	190		
Open studies	1117	90	1027	517	116[†]
Post marketing	0		0	0	0
Compassionate use	0		0	0	0

* This refers to patients who completed at least 24 weeks continuous exposure to lumacaftor/ivacaftor combination therapy.

[†] Patients who completed at least 24 weeks in Study 105 having completed 24 weeks of lumacaftor/ivacaftor therapy in Study 103 or 104.

Adverse events

Pooled placebo-controlled Phase III studies

Nearly all subjects in the LUM/IVA (95.8%) and placebo (95.9%) groups had AEs. The incidence of AEs leading to study drug discontinuation was higher in the LUM/IVA group (4.2%) than the placebo group (1.6%). The incidence of adverse events leading to study drug interruption was 5.7% in the LUM/IVA group and 6.8% in the placebo group; see table below. The population enrolled in the Phase III studies had numerous concomitant morbidities and concomitant medications as is to be expected in patients with cystic fibrosis. Therefore assessment of causality of adverse events poses a particular problem in this population.

Summary of Adverse Event Incidence: Pooled Placebo-Controlled Phase III Studies, Safety Set

		LUM/IVA		
Subjects With:	Placebo N = 370 n (%)	LUM 600mg qd/ IVA 250mg q12h N = 369 n (%)	LUM 400mg q12h/ IVA 250mg q12h N = 369 n (%)	Total LUM/IVA N = 738 n (%)
Total number of Adverse Events[a]	2132	2167	2130	4297
Any adverse events	355 (95.9)	356 (96.5)	351 (95.1)	707 (95.8)
Adverse events leading to treatment discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)
Adverse events leading to treatment interruption	25 (6.8)	20 (5.4)	22 (6.0)	42 (5.7)
Grade 3 or 4 adverse events	59 (15.9)	57 (15.4)	45 (12.2)	102 (13.8)
Serious adverse events	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
Related serious adverse events[b]	8 (2.2)	8 (2.2)	14 (3.8)	22 (3.0)
Adverse events leading to death	0	0	0	0

AE: adverse event; IVA: ivacaftor; LUM: lumacaftor; LUM/IVA: lumacaftor/ivacaftor; q12h: every 12 hours; qd: daily; SAE: serious adverse event; Grade 3 or 4: severe or life-threatening.
Note: When summarizing n (%) subjects, multiple events were counted only once in that category.
a For the calculation of the total number of events, subjects with multiple events within a category were counted multiple times in that category.
b Related adverse events include related, possibly related, and missing categories.

The most common AEs (incidence of at least 15% in any treatment group) were infective pulmonary exacerbation of CF, cough, headache, and sputum increased. AEs with an incidence at least 3% higher in the total LUM/IVA group than the placebo group were dyspnoea (14.0% versus 7.8%), respiration abnormal (9.8% versus 5.9%), flatulence (6.0% versus 3.0%), and rash (5.6% versus 1.9%). AEs for which the incidence in the total LUM/IVA group was ≥5% and the difference in incidence was ≥1% higher compared with the placebo group were dyspnoea, diarrhoea, nausea, respiration abnormal, oropharyngeal pain, upper respiratory tract infection, flatulence, rhinitis, rash, rhinorrhoea, and vomiting. The number of subjects with AEs considered by the investigator to be related to the study drug was higher in the total LUM/IVA group (48.0%) compared with the placebo group (34.9%). The majority of AEs across all 3 treatment groups were mild or moderate in severity. An analysis of the incidence of AEs by 8-week intervals demonstrated that the onset of the majority of new adverse events was generally higher in the first 8 weeks of treatment in both the LUM/IVA and placebo groups. No adverse events increased in incidence more than 2% after the first 8 weeks.

Phase I Studies in Healthy Volunteers

Data from 9 Phase 1 studies in healthy volunteers were pooled, regardless of study drug dose or treatment duration. Data were provided for all treatment groups: placebo, LUM monotherapy, ivacaftor monotherapy, lumacaftor in combination with ivacaftor (LUM/IVA), and lumacaftor in combination with ivacaftor and a drug:drug interaction (DDI) drug (LUM/IVA DDI).

Adverse Events with an Incidence of at least 3% in Subjects who Received Lumacaftor in Combination with Ivacaftor (With or Without a DDI Drug) by Preferred Term

	Treatment Group[a]						
Preferred Term	Placebo N = 47 n (%)	LUM Monotherapy N = 163 n (%)	IVA Monotherapy N = 52 n (%)	LUM/IVA[b] N = 173 n (%)	LUM/IVA DDI[b] N = 53 n (%)	Any LUM[c] N = 287 n (%)	Overall[d] N = 314 n (%)
Subjects with any AEs	27 (57.4)	99 (60.7)	34 (65.4)	95 (54.9)	17 (32.1)	180 (62.7)	206 (65.6)
Diarrhoea	3 (6.4)	10 (6.1)	3 (5.8)	30 (17.3)	2 (3.8)	40 (13.9)	46 (14.6)
Headache	11 (23.4)	25 (15.3)	12 (23.1)	13 (7.5)	5 (9.4)	41 (14.3)	60 (19.1)
Cough	0	1 (0.6)	9 (17.3)	12 (6.9)	0	12 (4.2)	21 (6.7)
Nasal congestion	2 (4.3)	6 (3.7)	0	8 (4.6)	0	14 (4.9)	16 (5.1)
Pharyngitis	3 (6.4)	4 (2.5)	3 (5.8)	6 (3.5)	0	10 (3.5)	16 (5.1)
Abdominal pain	4 (8.5)	1 (0.6)	0	5 (2.9)	2 (3.8)	8 (2.8)	12 (3.8)
Nausea	5 (10.6)	7 (4.3)	2 (3.8)	3 (1.7)	3 (5.7)	11 (3.8)	18 (5.7)
Pain in extremity	2 (4.3)	6 (3.7)	0	1 (0.6)	2 (3.8)	8 (2.8)	10 (3.2)
Hand dermatitis	0	0	0	0	2 (3.8)	2 (0.7)	2 (0.6)

AE: adverse event; DDI: drug-drug interaction; IVA: ivacaftor; LUM: lumacaftor.
Notes: AEs are sorted by decreasing frequency in the 'LUM/IVA' column. Percentages were calculated relative to the number of subjects in the Safety Set. The Safety Set was defined as all subjects who received any amount of study drug. Subjects with multiple events within a category were counted only once in that category.

a Subjects may be counted in more than one treatment group.
b The 'LUM/IVA' column includes unique subjects who received lumacaftor in combination with ivacaftor without a DDI drug. The 'LUM/IVA DDI' column includes unique subjects who received lumacaftor in combination with ivacaftor and a DDI drug.
c The 'Any LUM' column includes unique subjects who received either lumacaftor monotherapy, lumacaftor in combination with ivacaftor, or lumacaftor in combination with ivacaftor and a DDI drug.
d The 'Overall' column includes unique subjects with exposure to any study drug.

The majority of AEs were mild or moderate in severity. Of the 95 subjects in the LUM/IVA group who had an AE, 1 subject (0.6%) had a severe adverse event (diarrhoea). Of the 27 subjects in the placebo group who had an adverse event, 1 subject (2.1%) had a severe adverse event (diarrhoea). No subjects in the LUM/IVA, LUM/IVA DDI, or placebo groups had a life-threatening adverse event. Of the 95 subjects in the LUM/IVA group who had an AE, 5 subjects (2.9%) had an adverse event considered to be related to study drug, and 52 subjects (30.1%) had an adverse event considered to be possibly related to study drug. Of the 27 subjects in the placebo group who had an AE, 3 subjects (6.4%) had an AE considered to be related to study drug, and 12 subjects (25.5%) had an AE considered to be possibly related to study drug. The most commonly reported AEs considered to be related or possibly related to study drug were diarrhoea, upper abdominal pain, increased liver transaminases, vomiting, headache and dyspnoea.

Serious adverse event / deaths / other significant events

Pooled placebo-controlled Phase III studies

There were no deaths during the placebo-controlled Phase 3 studies. One subject from the LUM 400 mg q12h/IVA 250 mg q12h group of study 103 (Subject xxxx) rolled over into study 105 and had an SAE (infective pulmonary exacerbation of cystic fibrosis) with fatal outcome approximately 1 year after starting study drug and 22 days after study drug was withdrawn due to the AE. This event was considered unrelated to study drug by the investigator. The incidence of SAEs was higher in the placebo (28.6%) group compared with the total LUM/IVA group (20.1%). The incidence of SAEs was lower in the LUM 400 mg q12h/IVA 250 mg q12h group (17.3%) compared with the LUM 600 mg qd/ IVA 250 mg q12h group (22.8%). The most commonly reported SAE was infective pulmonary exacerbation of cystic fibrosis but the inverse dose response suggests that treatment with lumacaftor/ivacaftor may actually decrease the risk of an exacerbation of cystic fibrosis. The incidence of SAEs considered related to study drug was similar in the placebo (2.2%) and total LUM/IVA groups (3.0%). Related SAEs that occurred in 2 or more subjects overall were: blood creatinine phosphokinase increased (0.3% total LUM/IVA, 0% placebo), liver function test abnormal (0.3% total LUM/IVA, 0% placebo), bronchospasm (0.3% total LUM/IVA, 0% placebo), haemoptysis (0.3% total LUM/IVA, 0.5% placebo), infective pulmonary exacerbation of cystic

fibrosis (0.1% total LUM/IVA, 1.1% placebo), nephrolithiasis (0.3% total LUM/IVA, 0% placebo), and rash (0.3% total LUM/IVA, 0% placebo)

Phase I Studies in Healthy Volunteers

No deaths occurred in the pooled Phase 1 studies. Overall, 4 (1.3%) subjects had a Grade 3 or 4 AE. One subject (0.6%) in the LUM/IVA group and 1 subject (2.1%) in the placebo group had a severe AE of diarrhoea. Other Grade 3 or 4 AEs that occurred during the pooled Phase 1 studies were lipase increased and rhabdomyolysis. The only SAE thought to be related to study drug was rhabdomyolysis.

Laboratory findings

In general, there were few clinically relevant abnormal laboratory findings. There is a consistent elevation of liver enzymes in the active treatment arms in the Phase III studies and of creatinine phosphokinase. In the latter there appears to be a dose response element associated with lumacaftor with a higher percentage of patients in the lumacaftor 400mg q12h/ivacaftor 250mg q12h group (7.3%) than in the lumacaftor 600mg qd/ivacaftor 250mg q12h group (3.8%) reporting elevated creatinine phosphokinase.

The reports of increased CPK were requested by the CHMP to be reviewed but no possible mechanism by which the combination of lumacaftor and ivacaftor might cause an increase in blood CPK has been found.

Adverse events of special interest (AESI)

Liver-related adverse events: Mild and moderate elevations in ALT and/or AST were observed in a small number of subjects in Phase I/II studies involving LUM/IVA. Such transaminase elevations were generally not progressive and were not associated with elevations in total bilirubin. Elevations in liver function test values were generally mild and transient. The majority of subjects in the LUM/IVA group had maximum ALT and AST levels of ≤3 × ULN. Only 2 subjects (1.2%) in the LUM/IVA group had maximum ALT or AST of >3 to ≤5 × ULN. In the Phase III studies the incidence of elevated transaminases or hepatobiliary disorder adverse events was similar in the total LUM/IVA group (5.7%) and the placebo group (5.4%). Within the active treatment groups, the incidence was similar between the LUM 600 mg qd/ IVA 250 mg q12h group (5.4%) and the LUM 400 mg q12h/IVA 250 mg q12h group (6.0%). The AESIs of elevated transaminases with the highest overall incidence were ALT increased (1.9% in the total LUM/IVA group and 2.4% in the placebo group) and AST increased (2.0% in the total LUM/IVA group and 2.2% in the placebo group).

The majority of elevated transaminases or hepatobiliary disorder adverse events were mild or moderate in severity. Five subjects in the total LUM/IVA group (3 subjects in the LUM 600 mg qd/IVA 250 mg q12h group and 2 subjects in the LUM 400 mg q12h/IVA 250 mg q12h group) and 1 subject in the placebo group had elevated transaminases or hepatobiliary disorder adverse events that were considered severe. Seven (7) subjects (0.9%) in the total LUM/IVA group (4 subjects in the LUM 600 mg qd/ IVA 250 mg q12h and 3 subjects in the LUM 400 mg q12h/IVA 250 mg q12h group) had SAEs of elevated transaminases or hepatobiliary disorders.

Raised transaminases were seen in patients in the placebo arm as well as in patients receiving LUM/IVA and there was only a small increase in incidence in raised transaminases in the active treatment arms. Of the seven patients who developed SAEs related to elevated transaminases of hepatobiliary events, in four cases the event resolved on stopping or interrupting treatment while in three the event did not resolve. Therefore there was no consistent positive de-challenge but a causal relationship between lumacaftor/ivacaftor and raised hepatic transaminases cannot be ruled out. This adverse event has been reflected in the SmPC of Orkambi. As a safety measure, monitoring of LFTs is advised before starting treatment with lumacaftor/ivacaftor and at regular intervals during treatment.

Elevated creatinine phosphokinase (CPK) was noted in several subjects with increased transaminases, hence, a review of CPK and transaminases was performed. Overall, no clear difference between

transaminases and CPK in subjects receiving LUM/IVA compared with placebo was observed. In the pooled placebo-controlled Phase III studies, 5.4% of subjects in the placebo group and 5.6% of subjects in the total LUM/IVA group had an adverse event of blood CPK increased. The overall incidence of CPK >3 × ULN to ≤10 × ULN and >10 × ULN was similar in the total LUM/IVA group (4.0% and 2.3%) compared with the placebo group (4.9% and 2.7%). Overall, 14 subjects with AST (>3 × ULN) also had marked CPK elevations (>10 × ULN), but the incidence was similar between the total LUM/IVA group (9 subjects [1.2%]) and placebo group (5 subjects [1.4%]).

Respiratory adverse events: The most common AEs during the lumacaftor monotherapy and lumacaftor and ivacaftor combination therapy in study 102 were cough, CF lung, headache, productive cough, upper respiratory tract infection, nausea, haemoptysis, respiration abnormal, and dyspnoea. Respiration abnormal and dyspnoea occurred more commonly in subjects who received higher doses of lumacaftor monotherapy compared with lumacaftor in combination with ivacaftor or placebo. These AEs were primarily observed within the first 3 days of lumacaftor monotherapy and were generally mild to moderate, resolving with continued dosing.

In the Phase III studies, higher percentage of subjects had respiratory AESIs in the total LUM/IVA group (194 subjects [26.3%]) compared with the placebo group (63 subjects [17.0%]). The incidence of respiratory AESIs was similar in the LUM 600 mg qd/IVA 250 mg q12h group (26.8%) and LUM 400 mg q12h/ IVA 250 mg q12h group (25.7%). The AESI of respiratory symptoms with the highest overall incidence was dyspnoea (11.9%), which had a higher incidence in the total LUM/IVA group (14.0% [14.9% in the LUM 600 mg qd/IVA 250 mg q12h group and 13.0% in the LUM 400 mg q12h/IVA 250 mg q12h group]) compared with the placebo group (7.8%). In the extension study 105, a total of 141 (13.7%) subjects had AESIs of respiratory symptoms. The incidence of AESIs of respiratory symptoms was higher in subjects who received placebo in the parent studies compared with subjects who received active treatment in the parent study. There is a consistent pattern across the Phase III studies of an increased incidence of dyspnoea and respiration abnormal (generally chest tightness or bronchospasm/wheezing) associated with lumacaftor/ivacaftor combination therapy when compared with placebo. This pattern is the same in subgroup analyses of age and severity of disease and was not mitigated by prior use of bronchodilators, which were used by over 95% of subjects. However there is no consistent pattern of an increased incidence in respiratory adverse events with increasing dose of lumacaftor in combinations with ivacaftor. The respiratory adverse events of dyspnoea and bronchospasm were generally mild to moderate in severity, appeared to be associated with initiation of treatment with lumacaftor/ivacaftor and, in the majority of subjects, did not require cessation of therapy.

Ophthalmological effects: Due to the nonclinical finding of a dose-related increase in lens opacities in juvenile rats exposed to multiple doses of ivacaftor monotherapy, ophthalmologic examinations were conducted during the ivacaftor clinical development program. In the lumacaftor/ivacaftor development programme, ophthalmological examinations were conducted at screening in studies 103 and 104 in order to exclude patients with pre-existing cataracts. No follow-up examinations were conducted and therefore the development of cataracts following lumacaftor/ivacaftor therapy is reliant on the reporting of AEs. The Applicant maintains that there is no evidence of a risk in humans, particularly in subjects aged 12 years and older as were the subjects enrolled in Studies 103 and 104. Lumacaftor/ivacaftor is not proposed to be licensed for use in children less than 12 years of age and the risk of cataract appears to be confined to this young age group. Cataract is addressed as an important potential risk in the RMP.

Menstrual abnormalities: The data from the lumacaftor monotherapy and lumacaftor/ivacaftor combination clinical development programme strongly suggest that lumacaftor has an effect on hormonal contraceptive effectiveness; although there is also some suggestion that lumacaftor may have a direct effect on menstrual irregularities. A mechanism by which lumacaftor could directly affect menstruation is not known but it is biologically plausible that lumacaftor, as a strong CYP3A inducer, would reduce the effectiveness of hormonal contraceptives. Appropriate warnings have been included in the SmPC.

QTc prolongation: A thorough QT Study was performed to determine the effect of a therapeutic and a supratherapeutic dose of lumacaftor in combination with ivacaftor on the QT/QTc interval. There is no evidence that lumacaftor in combination with ivacaftor prolongs the QTc interval to a clinically relevant extent. The supratherapeutic dose used in this study gave an exposure to lumacaftor that is significantly higher than the exposure in patients with cystic fibrosis even in the presence of moderate hepatic impairment or if given concomitantly with CYP3A inhibitors. These results therefore give reassurance regarding the arrhythmic potential of lumacaftor/ivacaftor.

Safety in special populations

Age: In the pooled analysis of placebo-controlled Phase 3 studies, subgroup analyses of the incidence of adverse events were assessed by age group (subjects ≥18 years of age and subjects ≥12 to <18 years of age). Of the 1108 subjects who received study drug in the pooled, placebo-controlled Phase 3 program, 290 subjects were aged ≥12 to <18 years of age. In general, the safety profile of the total LUM/IVA and placebo groups was similar in subjects ≥12 to <18 years of age and subjects ≥18 years of age. There are no safety issues that are peculiar to any age group. It is accepted that there are no data in the elderly population (>64 years) as cystic fibrosis leads to a shortened life expectancy.

Gender: Approximately equal numbers of males and females were enrolled in the pooled placebo-controlled Phase 3 studies. The incidence of AEs was higher for females than for males in all treatment groups. However, the overall safety profile was similar for both sexes. AEs that were at least 5% more common in females compared with males were infective pulmonary exacerbation of cystic fibrosis, cough, dyspnoea, sputum increased, and nausea. These events had an increased incidence in both the placebo and total LUM/IVA groups for females compared with males, so the increase in frequency is unlikely to be associated with LUM/IVA therapy, but rather suggests that these events are more common in females. Consistent with the overall trend for the pooled placebo-controlled Phase III analysis (males and females), there was a decreased incidence of infective pulmonary exacerbation of cystic fibrosis and cough for male or female subjects in the total LUM/IVA group compared with the placebo group.

Percentage predicted FEV1 at baseline: The pooled placebo-controlled Phase 3 studies enrolled subjects with percent predicted FEV1 ≥40 and ≤90 of normal for age, sex, and height at screening. Subjects were stratified at randomization for percent predicted FEV1 <70 and ≥70 at screening. The range of percent predicted FEV1 at baseline was 31.1% to 96.5% in the total LUM/IVA group and 33.9% to 99.8% in the placebo group. To assess the impact of percent predicted FEV1 on safety, subgroup analyses were conducted to assess the safety of lumacaftor in combination with ivacaftor in subjects with percent predicted FEV1 <70 or ≥70 and in subjects with percent predicted FEV1 <40 at baseline. The majority of subjects enrolled in the pooled placebo-controlled Phase 3 studies had percent predicted FEV1 <70 at screening; there were no clinically meaningful differences in the pattern of AEs related to severity of lung disease at screening.

Hepatic impairment (Study 010): Both lumacaftor and ivacaftor are mainly metabolised via the hepatic route. Lumacaftor is a strong inducer of CYP3A and ivacaftor is a substrate of CYP3A. Study 010 was conducted to assess the impact of moderate hepatic impairment (Child-Pugh B) on the PK of lumacaftor and ivacaftor combination treatment. All 23 subjects enrolled received at least 1 dose of (LUM 200 mg q12h/IVA 250 mg q12h); 11 (91.7%) of the subjects with moderate hepatic impairment and 11 (100%) of the healthy subjects completed dosing with study drug for 10 days. In patients with moderate hepatic impairment, exposure at steady state (AUC_T) to lumacaftor and ivacaftor was increased by approximately 50% and C_{max} by 30%. Advice is given in section 4.2 of the SmPC to decrease the dose to a maximum daily dose of lumacaftor 600 mg/ivacaftor 375 mg in patients with moderate hepatic impairment. Advice is also given to decrease the dose further in patients with more severe hepatic impairment and to use only if the benefits outweigh the risks.

In study 010 two healthy volunteers had raised liver enzymes after 10 days dosing with lumacaftor/ivacaftor. The liver enzyme levels returned to normal after discontinuing study medication without further treatment, which suggests a causal relationship between the raised liver enzymes and lumacaftor/ivacaftor. Warnings are included in section 4.4 of the SmPC regarding the possibility of elevated liver transaminases and advising that LFTs should be checked before initiating lumacaftor/ivacaftor therapy and at regular intervals during therapy. Hepatobiliary events are also included in the RMP as a safety concern.

Renal impairment: In an absorption, distribution, metabolism, and excretion (ADME) study (Study 004), there was minimal elimination of lumacaftor and its metabolites in urine (only 8.6% of total radioactivity was recovered in the urine, with 0.18% as unchanged parent). These results suggest that renal clearance is likely to play a minimal role in the elimination of lumacaftor and pharmacokinetic studies in subjects with renal impairment have not been performed.

Pregnancy and lactation: The effects of lumacaftor on conception, pregnancy, and lactation in humans are not known as no adequate and well-controlled studies of ivacaftor in pregnant or lactating women have been conducted. Results from embryo-fetal development (EFD) reproductive toxicology studies in pregnant rats and rabbits indicated that lumacaftor is not a teratogen. There were 5 pregnancies in the Phase 3 studies and all 5 subjects were on active treatment. Given the limited data on the outcomes after drug exposure during pregnancy, lumacaftor should not be used during pregnancy unless the potential benefit justifies the potential risk. Lumacaftor and ivacaftor are excreted into the milk of lactating female rats. The SmPC summarizes all relevant nonclinical data on fertility, pregnancy and lactation and warns to only use in pregnancy or lactation when clearly needed.

Immunological events: There was one case of reported drug hypersensitivity that led to study drug discontinuation in the Phase III placebo-controlled studies. This was a patient in the lumacaftor 400mg q12h/ivacaftor 250mg q12h group.No other immunological events are listed in the summary of clinical safety. Hypersensitivity to the active substance or to any of the excipients is a contraindication in section 4.3 of the SmPC.

Safety related to drug-drug interactions and other interactions

CYP3A inhibitors and inducers: The concomitant use of lumicaftor/ivacaftor with strong inducers of CYP3A is not recommended as ivacaftor systemic exposure will be decreased with possible loss of efficacy. Strong inhibitors of CYP3A, such as itraconazole, increase ivacaftor exposure but due to the induction of CYP3A by lumacaftor, the net ivacaftor exposure does not exceed that when given in the absence of lumacaftor at a dose of 150 mg q12h.

Bronchodilators: Study 009 was an open-label study designed to examine the effect of ciprofloxacin, itraconazole, and rifampin on the PK of lumacaftor in combination with ivacaftor in healthy adult subjects. An asymptomatic, generally mild decline in FEV1 was noted in subjects within 4 hours of treatment with lumacaftor 200mg q12h in combination with ivacaftor 250 mg q12h. None of the subjects had an SAE, required treatment with concomitant medications, or had long-term sequelae as a result of the decline in FEV1. Given the acute nature of this finding, it was considered likely that there was an element of bronchoconstriction contributing to the decline in FEV1. AEs of dyspnoea and bronchospasm appear to occur at initiation of lumacaftor/ivacaftor therapy and generally resolve without discontinuing therapy.

Discontinuation due to adverse events

The adverse events were generally mild to moderate in severity, tended to occur early in treatment and mainly resolved without discontinuing treatment with lumacaftor/ivacaftor.

Long-term safety data

Study 105 is an ongoing Phase III rollover for Studies 103, 104, and 102 Cohort 4 designed to evaluate the long-term safety and efficacy of LUM/IVA in subjects aged 12 years and older with CF, homozygous (Part A) or heterozygous (Part B) for the *F508del-CFTR* mutation. A total of 1108 subjects received at least 1 dose of study drug (placebo or LUM/IVA) in the parent Studies 103 or 104. Of these subjects, 1031 subjects were enrolled in the Part A Treatment Cohort and 19 subjects were enrolled in Part A Observational Cohort. Of these subjects, 334 subjects who received LUM 600 mg qd/ IVA 250 mg q12h and 341 subjects who received LUM 400 mg q12h/IVA 250 mg q12h in the previous study continued to receive the same treatments in Study 105. Among the subjects who received placebo in the previous study, 179 subjects were randomized to receive LUM 600 mg qd/IVA 250 mg q12h and 176 subjects were randomized to receive LUM 400 mg q12h/IVA 250 mg q12h.

There was a lack of overall evidence of clinical benefit in the subjects in Part B of Study 105 so all subjects in Part B were notified and Vertex strongly recommended that all subjects from Part B were discontinued from the study. Two dose levels of lumacaftor (400 mg q12h or 600 mg qd) are being evaluated in combination with ivacaftor 250 mg q12h over a 96-week treatment period. At the time of the original MAA submission, enrolment in Study 105 was complete and the study was ongoing. The Applicant has provided an addendum to the Summary of Clinical Safety with a Second Interim Analysis of safety from Study 105 (IA2).A total of 1092 subjects in the 103/104 Safety Set received at least 1 dose of LUM/IVA in Study 105. Of the subjects who received LUM/IVA in the previous study, the mean cumulative treatment duration was similar between the LUM 600 mg daily (qd)/IVA 250 mg every 12 hours (q12h) group (LUM 600 group; 418.5 days) and LUM 400 mg q12h/IVA 250 mg q12h group (LUM 400 group; 420.7 days). Of the subjects who received placebo in the previous study, the mean treatment duration was similar between the placebo/LUM 600 group (279.6 days) and placebo/LUM 400 group (281.5 days).

Most subjects received at least 24 weeks of LUM/IVA (1015 subjects [92.9%] overall) with the majority receiving at least 48 weeks of LUM/IVA (683 subjects [62.5%] overall). Of the subjects who received LUM/IVA in the previous study, the percentage of subjects who were exposed to LUM/IVA for ≥48 weeks was similar between the LUM 600 (84.6%) and the LUM 400 (86.1%) groups. Of the subjects who received placebo in the previous study, the percentage of subjects who were exposed to LUM/IVA for ≥48 weeks was similar between placebo/LUM 600 (14.0%) and the placebo/LUM 400 (15.9%) groups

Summary of Exposure, Active Treatment Period, Part A (103/104 Safety Set)

	L600qd+I N = 370	Pbo/ L600qd+I N = 178	L400q12h+I N = 368	Pbo/ L400q12h+I N = 176	Overall N = 1092
Total exposure (patient years)	**424.0**	**136.2**	**423.9**	**135.6**	**1119.7**
Exposure duration (days)					
n	370	178	368	176	1092
Mean (SD)	418.5 (123.89)	279.6 (67.22)	420.7 (117.69)	281.5 (70.10)	374.5 (124.96)
SE	6.44	5.04	6.14	5.28	3.78
Median	450.0	284.5	446.0	288.5	431.0
Min, max	1, 564	1, 389	1, 585	13, 388	1, 585
Exposure duration, n (%)					
≥1 dose	370 (100.0)	178 (100.0)	368 (100.0)	176 (100.0)	1092 (100.0)
≥8 weeks	356 (96.2)	174 (97.8)	357 (97.0)	171 (97.2)	1058 (96.9)
≥16 weeks	353 (95.4)	168 (94.4)	352 (95.7)	167 (94.9)	1040 (95.2)
≥24 weeks	346 (93.5)	166 (93.3)	341 (92.7)	162 (92.0)	1015 (92.9)
≥32 weeks	326 (88.1)	162 (91.0)	329 (89.4)	160 (90.9)	977 (89.5)
≥40 weeks	319 (86.2)	98 (55.1)	322 (87.5)	102 (58.0)	841 (77.0)
≥48 weeks	313 (84.6)	25 (14.0)	317 (86.1)	28 (15.9)	683 (62.5)
≥56 weeks	310 (83.8)	0	314 (85.3)	0	624 (57.1)
≥64 weeks	191 (51.6)	0	182 (49.5)	0	373 (34.2)
≥72 weeks	56 (15.1)	0	50 (13.6)	0	106 (9.7)
≥80 weeks	2 (0.5)	0	2 (0.5)	0	4 (0.4)

Notes: Duration of study drug exposure (days) = last dose date of the analysis period - first dose date of the same analysis period + 1. Active treatment exposure period started from the initial dose of the active treatment to the last dose of study drug or date of data cut, whichever was earlier. Time between the last dose of study drug in the previous study and the initial dose of study drug in Study 105 was excluded from the exposure duration for the Active Treatment Period.

Overview of adverse events (103/104 Safety set)

	0-24 weeks on LUM/IVA			24-48 weeks on LUM/IVA			0-48 weeks on LUM/IVA			>48 weeks on LUM/IVA		
Category	**L600qd+I N = 548**	**L400q12h+I N = 544**	**Overall N = 1092**	**L600qd+I N = 518**	**L400q12h+I N = 508**	**Overall N = 1026**	**L600qd+I N = 548**	**L400q12h+I N = 544**	**Overall N = 1092**	**L600qd+I N = 340**	**L400q12h+I N = 347**	**Overall N = 687**
Number of AEs (total)	3035	2971	6006	1685	1582	3267	4720	4553	9273	603	579	1182
Subjects with any AEs	526 (96.0)	520 (95.6)	1046 (95.8)	418 (80.7)	416 (81.9)	834 (81.3)	538 (98.2)	532 (97.8)	1070 (98.0)	207 (60.9)	209 (60.2)	416 (60.6)
Subjects with Grade 3/4 AEs	77 (14.1)	66 (12.1)	143 (13.1)	46 (8.9)	40 (7.9)	86 (8.4)	108 (19.7)	100 (18.4)	208 (19.0)	34 (10.0)	24 (6.9)	58 (8.4)
Subjects with AEs by maximum relationship												
Related	26 (4.7)	26 (4.8)	52 (4.8)	9 (1.7)	1 (0.2)	10 (1.0)	34 (6.2)	26 (4.8)	60 (5.5)	3 (0.9)	0	3 (0.4)
Possibly related	213 (38.9)	241 (44.3)	454 (41.6)	83 (16.0)	77 (15.2)	160 (15.6)	236 (43.1)	271 (49.8)	507 (46.4)	19 (5.6)	15 (4.3)	34 (4.9)
Unlikely related	112 (20.4)	111 (20.4)	223 (20.4)	115 (22.2)	122 (24.0)	237 (23.1)	111 (20.3)	108 (19.9)	219 (20.1)	64 (18.8)	58 (16.7)	122 (17.8)
Not related	175 (31.9)	142 (26.1)	317 (29.0)	203 (39.2)	209 (41.1)	412 (40.2)	149 (27.2)	122 (22.4)	271 (24.8)	115 (33.8)	129 (37.2)	244 (35.5)
Missing	0	0	0	8 (1.5)	7 (1.4)	15 (1.5)	8 (1.5)	5 (0.9)	13 (1.2)	6 (1.8)	7 (2.0)	13 (1.9)
Subjects with AEs by maximum severity												
Mild	201 (36.7)	190 (34.9)	391 (35.8)	158 (30.5)	174 (34.3)	332 (32.4)	142 (25.9)	144 (26.5)	286 (26.2)	86 (25.3)	87 (25.1)	173 (25.2)
Moderate	248 (45.3)	264 (48.5)	512 (46.9)	212 (40.9)	202 (39.8)	414 (40.4)	288 (52.6)	288 (52.9)	576 (52.7)	86 (25.3)	97 (28.0)	183 (26.6)
Severe	76 (13.9)	65 (11.9)	141 (12.9)	43 (8.3)	40 (7.9)	83 (8.1)	105 (19.2)	99 (18.2)	204 (18.7)	33 (9.7)	23 (6.6)	56 (8.2)
Life-threatening	1 (0.2)	1 (0.2)	2 (0.2)	3 (0.6)	0	3 (0.3)	3 (0.5)	1 (0.2)	4 (0.4)	1 (0.3)	1 (0.3)	2 (0.3)
Missing	0	0	0	2 (0.4)	0	2 (0.2)	0	0	0	1 (0.3)	1 (0.3)	2 (0.3)
Subjects with AEs leading to treatment discontinuation	24 (4.4)	27 (5.0)	51 (4.7)	17 (3.3)	7 (1.4)	24 (2.3)	40 (7.3)	34 (6.3)	74 (6.8)	2 (0.6)	1 (0.3)	3 (0.4)
Subjects with AEs leading to treatment interruption	32 (5.8)	41 (7.5)	73 (6.7)	22 (4.2)	17 (3.3)	39 (3.8)	48 (8.8)	56 (10.3)	104 (9.5)	7 (2.1)	6 (1.7)	13 (1.9)
Subjects with serious AEs	122 (22.3)	103 (18.9)	225 (20.6)	91 (17.6)	84 (16.5)	175 (17.1)	171 (31.2)	159 (29.2)	330 (30.2)	59 (17.4)	42 (12.1)	101 (14.7)
Subjects with related serious AEs[a]	11 (2.0)	22 (4.0)	33 (3.0)	8 (1.5)	6 (1.2)	14 (1.4)	19 (3.5)	27 (5.0)	46 (4.2)	4 (1.2)	0	4 (0.6)
Subjects with AEs leading to death	0	0	0	1 (0.2)	0	1 (0.1)	1 (0.2)	0	1 (0.1)	0	1 (0.3)	1 (0.1)

Notes: MedDRA version 17.1 was used. When summarizing the number of events, a subject with multiple events within a category was counted multiple times in that category.
When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Active Treatment Period started from the initial dose of active treatment to 28 days (inclusive) after the last dose of study drug, or date of data cut, whichever was earlier. AEs during the Active Treatment Period include AEs that increased in severity or that was newly developed within the corresponding period. 'N' is the number of subjects who entered the corresponding interval.

a Related serious AEs include related, possibly related and missing categories.

Summary of safety findings

Overall, the incidence of subjects with adverse events was lower during the 24-48 week interval (81.3%) compared to the 0-24 week interval (95.8%). In general, the incidence of subjects with adverse events was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed. During the 0-24 week interval, the most common adverse events (≥20% overall) were infective pulmonary exacerbation of CF (36.7%) and cough (29.5%). The incidences of these adverse events were lower during the 24-48 week interval (30.3% and 20.5%, respectively) and during the >48 week interval (19.9% and 14.0%, respectively). Treatment with LUM/IVA was well tolerated with continued treatment. The incidence of subjects with adverse events that led to treatment discontinuation was low (0-24 weeks: 4.7%; 24-48 weeks: 2.3%; >48 weeks: 0.4%).

- 4.4% of subjects in the L600qd+I group and 5.0% subjects in the L400q12h+I group had an adverse event that led to treatment discontinuation during the 0-24 week interval.
- 3.3% of subjects in the L600qd+I group and 1.4% subjects in the L400q12h+I group had an adverse event that led to treatment discontinuation during the 24-48 week interval.
- 0.6% of subjects in the L600qd+I group and 0.3% subjects in the L400q12h+I group had an adverse event that led to treatment discontinuation during the >48 week interval.

The most common adverse events that led to treatment discontinuation (those occurring in ≥5 subjects overall during any treatment interval) were respiration abnormal, dyspnea, blood creatine phosphokinase increased, and infective pulmonary exacerbation of CF. During the 24-48 week interval, the majority of subjects had adverse events that were considered mild or moderate (mild: 32.4%; moderate: 40.4%), which was consistent with the 0-24 week interval (mild: 35.8%; moderate: 46.9%). The incidence of subjects with severe adverse events was similar across all treatment intervals analyzed (0-24 weeks: 12.9%; 24-48 weeks: 8.1%; and >48 weeks: 8.2%). Life-threatening adverse events occurred in 2 subjects during the 0-24 week interval, 3 subjects during the 24-48 week interval, and 2 subjects during the >48 week interval. (Note that there were 4 unique subjects who had life-threatening adverse events during the 0-48 week interval.) In general, the severity of adverse events was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed. There were 2 deaths during the Active Treatment Period of Part A, one in the 0-24 week period and one in the 24-48 week period. One death was due to infective pulmonary exacerbation of CF leading to respiratory failure in the L400q12h+I group that occurred approximately 1 year after the first dose of LUM/IVA. The event was considered not related to the study drug by the investigator. The second death was due to a pulmonary exacerbation that occurred approximately 9 months after the first dose of LUM/IVA. The event was considered not related to study drug by the investigator. The incidences of subjects with at least 1 SAE during the 24-48 week (175 [17.1%] subjects) and >48 week (101 [14.7%] subjects) intervals were similar or lower compared to the 0-24 week interval (225 [20.6%] subjects).

The most common SAE was infective pulmonary exacerbation of CF, which occurred in 148 (13.6%) subjects during the 0-24 week interval, in 125 (12.2%) subjects during the 24-48 week interval, and in 75 (10.9%) subjects during the >48 week interval. The incidences of subjects with an AESI of elevated transaminases during the 24-48 week (24 [2.3%] subjects) and >48 week (6 [0.9%] subjects) intervals were similar or lower compared to the 0-24 week interval (60 [5.5%] subjects). The incidence of subjects

with an AESI of elevated transaminases was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed. The incidences of subjects with an AESI of respiratory symptoms during the 24-48 week (92 [9.0%] subjects) and >48 week (33 [4.8%] subjects) intervals were lower compared to the 0-24 week interval (252 [23.1%] subjects). The incidence of subjects with an AESI of respiratory symptoms was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed. The incidences of subjects with an AESI of reactive airways during the 24-48 week (33 [3.2%] subjects) and the >48 week (19 [2.8%] subjects) intervals were similar compared to the 0-24 week interval (69 [6.3%] subjects). The incidence of subjects with an AESI of reactive airways was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed. The incidences of subjects with an AESI of menstrual abnormality during the 24-48 week (17 [1.7%] subjects) and >48 week (3 [0.4%] subjects) intervals were similar compared to the 0-24 week interval (51 [4.7%] subjects). The incidence of subjects with an AESI of menstrual abnormality was similar between the L600qd+I group and the L400q12h+I group for all treatment intervals analyzed.

Overall, the incidence of subjects with PCS LFT elevations was low and similar between the 2 treatment groups (L600qd+I and L400q12h+I) and the 2 treatment intervals (0-24 weeks of LUM/IVA and 24-48 weeks of LUM/IVA). There were no clinically important trends attributable to lumacaftor in combination with ivacaftor identified from serum chemistry, haematology, coagulation, or urinalysis results.

There were no clinically important trends attributable to lumacaftor in combination with ivacaftor identified from vital signs, standard ECGs, pulse oximetry, or spirometry results. In general the incidence of AEs in the long term safety set was lower in the extension study (105) than in the placebo-controlled studies (103 and 104) and lower or similar in the 24-48 week period compared with the 0-24-week period. The Applicant has submitted additional long-term data from Study 105 including data on a larger number of subjects for at least 48 weeks exposure to lumacaftor/ivacaftor. These data do not give rise to any concerns about new or more severe adverse events occurring with long term exposure (up to 80 weeks) to lumacaftor/ivacaftor. In fact the rate of adverse events tends to decrease with longer duration of treatment.

Post marketing experience

There is no post marketing experience with Orkambi yet.

2.6.1. Discussion on clinical safety

A total of 1615 subjects were exposed to lumacaftor in combination with ivacaftor in Phase 1 through Phase 3 studies. Overall 738 subjects with CF were exposed to at least 1 dose of the LUM/IVA combination in the pooled placebo-controlled Phase 3 studies: 369 subjects received LUM 400 mg q12h/IVA 250 mg q12h and 369 subjects received LUM 600 mg qd/ IVA 250 mg q12h group. The median treatment duration in the phase 3 studies was 168 days (range: 1 to 182) for subjects in the total LUM/IVA group and 168 days (range: 7 to 181) for subjects in the placebo group. Long-term safety data are available from Study 105 for 674 subjects who continued on active treatment after receiving LUM/IVA for 24 weeks in Studies 103/104. The study is ongoing and is intended to evaluate the safety of LUM/IVA combination up to approximately 96 weeks. The results of the study will be submitted to the CHMP as it is captured in the RMP for Orkambi. Overall the safety database is considered adequate to evaluate the safety of the LUM/IVA combination therapy in different dose regimens in the short-term.

In general, the AEs seen in the clinical programme for lumacaftor/ivacaftor were as expected in the patient population with CF, and were mild to moderate in severity, occurred early in treatment and mainly resolved without discontinuing treatment with lumacaftor/ivacaftor. The pattern of AEs remained similar in the extension study with no evidence of increase in incidence or severity. Serious adverse events (SAEs) were reported in 28.6% of patients taking placebo and 20.1% of patients taking

lumacaftor/ivacaftor. Few of these were thought to be related to study medication, of which the most commonly reported were increased creatinine phosphokinase, liver function test abnormal, bronchospasm and rash. The main AEs that are thought to be related to treatment with lumacaftor/ivacaftor are respiratory (cough, dyspnoea, bronchospasm) and gastrointestinal (diarrhoea, nausea and vomiting). The most common AEs were signs/symptoms related to uncontrolled CF. Although infective pulmonary exacerbation of CF and cough were more represented in the placebo group, no clear evidence of significant benefit in disease control by LUM/IVA treatment was evident. Similarly, sputum production was only slightly increased in placebo compared to LUM/IVA-treated group. In the total LUM/IVA group, a major incidence of upper respiratory tract infections was also observed compared to placebo. This information was reflected in the SmPC in order to fully inform the prescribing physicians.

The majority of AEs occurred within the first 8 weeks of treatment both in the placebo as well as in the LUM/IVA-treated groups. However, it is noted that, the incidence of some respiratory AEs, i.e. cough, dyspnoea, and infective pulmonary exacerbation, decreased with time in the placebo group reaching approximately the frequency observed in the LUM/IVA-treated arms. This observation seems suggestive of adjustments in the background therapy in the placebo group which could impact on the interpretation of both safety as well as efficacy results.

Increase creatinine phosphokinase was reported in healthy volunteers taking lumacaftor/ivacaftor as well as in patients with CF and was associated with one case of rhabdomyolysis. In general, reports of raised liver enzymes are confounded by the fact that patients with CF are predisposed to liver abnormalities. However, a causal relationship cannot be ruled out and warnings are included in the SmPC with advice to monitor LFTs before instigating therapy with lumacaftor/ivacaftor and at regular intervals during therapy. This was considered sufficient by the CHMP.

Ophthalmological effects, particularly cataracts in children under the age of 12 years has been noted in association with ivacaftor exposure in juvenile rats and an observational study in children under the age of 12 years is ongoing. In the Phase III placebo-controlled studies for lumacaftor/ivacaftor, a baseline ophthalmological examination was performed to rule out pre-existing abnormalities, hence a warning statement on this potential risk was included in 4.4 of the SmPC. The applicant agreed to follow up the patients with an ophthalmological examination based on CHMP's request.

Menstrual abnormalities were reported in particular in patients taking the oral contraceptive pill (OCP) and are most likely due to induction of CYP3A enzymes by lumacaftor affecting the metabolism of the OCP. Therefore it is advised that non-hormonal contraception should be used when taking lumacaftor/ivacaftor and the SmPC includes this advice.

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

2.6.2. Conclusions on the clinical safety

Overall, the safety of the combination of LUM/IVA in the treatment of patients with CF who are homozygous for the F508del mutation in the CFTR gene is considered to be sufficiently characterised. The combination of lumacaftor and ivacaftor in the treatment of these patients has been shown to be generally well tolerated, with few serious adverse events related to study medication. Most AEs are mild in nature and resolve without treatment. The AEs that may potentially cause concern, such as raised liver enzymes or ophthalmological effects are balanced by appropriate risk minimisation measures.

During the course of the evaluation, the applicant submitted more data on long-term safety from Study 105, with 683 patients receiving lumacaftor/ivacaftor for at least 48 weeks. The data from the long-term safety study 105 has not demonstrated any increased safety concerns with longer duration of therapy.

The study is still ongoing and is planned for a longer total exposure so the applicant will submit a final report by December 2016 as described in the RMP.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan draft version 1.5 is acceptable. The MAA is requested to ensure that the comments made on the protocol for Study 108 are considered at the time of protocol finalisation, within 6 months.

The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.5 with the following content:

Safety concerns

Important identified risks	• Respiratory events
Important potential risks	• Hepatobiliary events • Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers • Concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index • Cataracts • Cardiac arrhythmias • Off-label use in children less than 12 years of age or in patients who are not homozygous for *F508del-CFTR* mutation
Missing information	• Use in pregnant and lactating women • Patients with percent predicted FEV_1 <40 • Long-term safety • Safety in patients with cardiac diseases • Use in patients with organ transplant • Effect of LUM/IVA on P-gp substrates • Potential off-target activity of M6-ivacaftor • Interaction potential between transporters and lumacaftor and/or ivacaftor • Potential environmental risk

CFTR: cystic fibrosis transmembrane conductance regulator; CYP3A: cytochrome P450 - enzyme subfamily 3A; FEV_1: forced expiratory volume in 1 second; LUM/IVA: lumacaftor in combination with ivacaftor; P-gp: permeability glycoprotein

Pharmacovigilance plan

Study / Activity Type, Category, and Title	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Study 105 (interventional, 2) A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With LUM/IVA in Subjects Aged 12 Years and Older With CF, Homozygous or Heterozygous for the *F508del-CFTR* Mutation	To evaluate the long-term safety and efficacy of LUM/IVA in subjects with CF	• Respiratory events • Hepatobiliary events • Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers • Concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index • Cataracts • Cardiac arrhythmias • Patients with percent predicted FEV_1 <40 • Long-term safety • Safety in patients with cardiac diseases	Started	Final Report: December 2016
Study 106 (interventional, 4) A Phase 3b, Open-Label Study to Evaluate LUM/IVA Therapy in Subjects 12 Years and Older With CF and Advanced Lung Disease, Homozygous for the *F508del-CFTR* Mutation	To provide LUM/IVA therapy to subjects 12 years and older with CF and advanced lung disease and who are homozygous for the *F508del* mutation on the *CFTR* gene	• Respiratory events • Hepatobiliary events • Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers • Concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index • Cataracts • Cardiac arrhythmias • Patients with percent predicted FEV_1 <40 • Safety in patients with cardiac diseases	Started	Final Report: March 2017
Study 108 (PASS) (noninterventional, 1) An Observational Study to Evaluate the Utilisation Patterns and Long-Term Effects of LUM/IVA Therapy in Patients with CF	To evaluate the long-term safety of LUM/IVA in patients with CF	• Hepatobiliary events • Cardiac arrhythmias • Off-label use • Use in pregnant women • Patients with percent predicted FEV_1<40 • Long-term safety • Safety in patients with cardiac diseases • Use in patients with organ transplant	Planned	Annual Reports: December 2017/2018/2019/ 2020 Final Report: December 2021

Study / Activity Type, Category, and Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Study 770-115 (interventional, 3) An Ocular Safety Study of Ivacaftor-Treated Pediatric Patients 11 Years or Younger With CF	To evaluate the prevalence and progression of cataracts in paediatric patients on ivacaftor monotherapy	• Cataracts	Started	Final Report: December 2016
Nonclinical, 2	Nonclinical studies to evaluate the potential off-target activity (receptor binding and ion channel activity) of M6-ivacaftor	• Potential off-target activity of M6-ivacaftor	Planned	Final Report: June 2016
Nonclinical, 2	In vitro studies to evaluate the potential inhibition of BCRP, OAT1, OAT3, OCT1, and OCT2 by lumacaftor and/or ivacaftor, and to evaluate if lumacaftor is a substrate for BCRP and MRP2	• Interaction potential between transporters and lumacaftor and/or ivacaftor	Planned	Final Report: December 2015
Nonclinical, 2	Nonclinical studies to evaluate potential environmental risk for lumacaftor and ivacaftor	• Potential environmental risk	Ongoing	Updated ERA Report: December 2015

CF: cystic fibrosis; BCRP: breast cancer resistance protein; CYP: cytochrome P450; ERA: environmental risk assessment; FEV_1: forced expiratory volume in 1 second; LUM/IVA: lumacaftor in combination with ivacaftor; MRP: multi-drug resistance protein; OAT: organic anion transporter; OCT: organic cation transporter; PASS: Post-authorisation Safety Study

In study 105, the applicant should explore the possibility of a longer (i.e. 5 years) follow up of the enrolled patients and provide results on the long-term efficacy and safety from this study population in the PSURs, following the frequency established in DIR 2001/83/EC Art 107c(2), as amended, unless otherwise stated in the EURD list.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Respiratory events	**Section 4.4** describes warnings of potential respiratory events during initiation of Orkambi therapy. Additional monitoring in patients with percent predicted FEV_1 <40 is recommended. **Section 4.8** describes respiratory events as an adverse reaction and described that these events are more common in patients with lower percent predicted FEV_1.	Not applicable
Hepatobiliary events	**Section 4.4** includes warnings of potential liver injury and transaminase elevations and precautions for use in patients with advanced liver disease. Recommendations are provided for transaminases and total bilirubin monitoring. Recommendations are provided to discontinue dosing in event of significant elevation of ALT or AST, with or without elevated bilirubin. **Section 4.2** describes posology recommendations for patients with hepatic impairment. **Section 4.8** describes the incidence, severity, and outcome of elevated transaminase levels and hepatobiliary events in clinical studies. **Section 5.2** describes PK properties in patients with moderately impaired hepatic function. Prescription-only medicine.	Not applicable
Concomitant use of LUM/IVA with strong CYP3A inhibitors or inducers	**Section 4.2** describes posology in case of CYP3A inhibitors coadministration. **Section 4.4** warns that concomitant use of CYP3A inducers may result in loss of Orkambi efficacy. **Section 4.5** details potential drug-drug interactions; concomitant use with strong CYP3A inducers is not recommended. Prescription-only medicine.	Not applicable
Concomitant use of LUM/IVA with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index	**Section 4.4** warns that Orkambi may decrease the therapeutic effect of medicinal products that are sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index; concomitant use with sensitive CYP3A substrates and CYP3A substrates with a narrow therapeutic index is not recommended. **Section 4.5** details this potential drug-drug interaction. Prescription-only medicine.	Not applicable
Cataracts	**Section 4.4** describes findings of non-congenital cataracts in paediatric patients treated with ivacaftor. Recommendations for eye examinations in paediatric patients are provided. **Section 5.3** summarizes preclinical data relevant to this potential risk. Prescription-only medicine.	Not applicable
Cardiac arrhythmias	The proposed activities are based on theoretical risk from nonclinical findings. It has not been confirmed in humans. **Section 5.3** describes preclinical findings of ivacaftor producing concentration-dependent inhibitory effect	Not applicable

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	on hERG tail currents; however, no ivacaftor-induced QT prolongation was observed in a dog telemetry study. No meaningful changes in QTc interval or blood pressure were seen in a thorough QT clinical study evaluating LUM/IVA, showing a lack of translation of these nonclinical findings to the clinic. Prescription-only medicine.	
Off-label use in children less than 12 years of age or in patients who are not homozygous for the *F508del-CFTR* mutation	**Section 4.1** specifies indication of Orkambi, excluding populations included in this potential risk. **Section 4.2** includes the recommendation in case of unknown genotype. The safety and efficacy of Orkambi in children aged less than 12 years have not been established. **Section 4.4** states that clinical efficacy was not established in patients who have the *F508del* mutation on one allele plus a second allele with a mutation predicted to result in the lack of CFTR production or that is not responsive to ivacaftor in vitro. Further, Orkambi has not been studied in patients with CF who have a gating (Class III) mutation in the *CFTR* gene on one allele, with or without the *F508del* mutation on the other allele. Because the exposure of ivacaftor is very significantly reduced when dosed in combination with lumacaftor, Orkambi should not be used for these patients. Prescription-only medicine.	Not applicable
Use in pregnant and lactating women	**Sections 4.6 and 5.3** summarize all known nonclinical data relevant to fertility, pregnancy and lactation and warn to only use in pregnancy or lactation when clearly needed. Prescription-only medicine.	Not applicable
Patients with percent predicted FEV_1 <40	**Section 4.4** states that additional monitoring is recommended in patients with percent predicted FEV_1 <40 during initiation of therapy. **Section 4.8** describes the higher incidence of respiratory events in patients with lower pre-treatment percent predicted FEV_1. **Section 5.1** describes the limited data for this patient population. Prescription-only medicine.	Not applicable
Long-term safety	**Sections 4.8** and **5.1** state that safety data is limited to 48 weeks. Long-term safety data is not available. Prescription-only medicine.	Not applicable
Safety in patients with cardiac diseases	The proposed activities are based on theoretical risk from nonclinical findings. It has not been confirmed in humans. **Section 5.3** describes preclinical findings of ivacaftor producing concentration-dependent inhibitory effect on hERG tail currents; however, no ivacaftor-induced QT prolongation was observed in a dog telemetry study. No meaningful changes in QTc interval or blood pressure were seen in a thorough QT clinical study evaluating LUM/IVA, showing a lack of translation of these nonclinical findings to the clinic. Prescription-only medicine.	Not applicable

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in patients with organ transplant	**Section 4.4** states that Orkambi has not been studied in this population; therefore, use is not recommended. **Section 4.5** includes a list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended. Prescription-only medicine.	Not applicable
Effect of LUM/IVA on P-gp substrates	**Section 4.5** describes the potential for Orkambi to affect digoxin, a P-gp substrate. Caution and appropriate monitoring are recommended. Prescription-only medicine.	Not applicable
Potential off-target activity of M6-ivacaftor	**Section 5.2** describes M1-ivacaftor and M6-ivacaftor as the main metabolites of ivacaftor. Prescription-only medicine.	Not applicable
Interaction potential between transporters and lumacaftor and/or ivacaftor	**Section 4.5** provides available data on interactions with transporters. Prescription-only medicine.	Not applicable
Potential environmental risk	**Section 5** of patient information leaflet provides instructions to patients on how to dispose Orkambi properly to protect environment. Prescription only medicine	Not applicable

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CYP3A: cytochrome P450 - enzyme subfamily 3A4; FEV_1: forced expiratory volume in 1 second; hERG: human ether-à-go-go-related gene; LUM/IVA: lumacaftor in combination with ivacaftor; PK: pharmacokinetic

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Orkambi (LUMACAFTOR / IVACAFTOR) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new

safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Lum 400mg bd/iva 250mg bd caused a significant improvement in the surrogate endpoint of ppFEV1 as early as 15 days of treatment which was maintained till 48 weeks. The extent of improvement in ppFEV1 was 1.68% and 2.63% at 24 weeks in study 103 and 104 respectively. This improvement was maintained at 48 weeks. An improvement in ppFEV1 of around 3.5% was seen at the second interim analysis of study 105 in patients who were on placebo in the pivotal studies but crossed-over to Lum 400mg bd/iva 250mg bd in study 105. The other key secondary endpoints on spirometry also showed similar improvements. The observed effects on the primary endpoint is small, but nevertheless can be accepted as clinically relevant as FEV1 is a significant predictor of mortality in cystic fibrosis and the benefits of higher FEV1 in CF patients have been described in the literature. Lum 400mg bd/iva 250 mg bd also caused a significant improvement in the gastrointestinal/nutritional endpoint of change in BMI from baseline in both pivotal studies and this benefit was seen to be sustained in study 105. Lum 400mg bd/iva 250 mg bd showed reductions in the clinical endpoint of number of pulmonary exacerbations including those that required hospitalization and those requiring IV antibiotic therapy. Consistent observations were seen with a reduction in the number of days with pulmonary exacerbations, of hospitalisation and on antibiotic therapy as compared to placebo. Increase in number of pulmonary exacerbations and decline in nutritional status have been correlated with mortality in CF and so a clinically relevant beneficial effect of lum/iva is anticipated based on the observed effects. In any case lum/iva reduced the need for IV antibiotics and hospitalization which directly reduces the overall treatment burden of these patients. The effects on secondary endpoints that were seen in the pivotal studies were maintained in the long-term extension study for up to 48 weeks treatment. In addition, patients who were on placebo in studies 103 and 104 and who were rolled over to active treatment in study 105 showed similar benefits to that observed in pivotal studies on both primary and secondary endpoints for the treatment duration of 24 weeks in study 105.

Uncertainty in the knowledge about the beneficial effects

Adequate supporting evidence from PD endpoints, which could provide evidence for sustained activity at the target mechanism of action is not available as there were limited PD assessments in the overall development of lum/iva. A relevant and significant effect on lum/iva on sweat chloride over and above lum monotherapy was not demonstrated and the effects of lum/iva on nasal potential difference have not been evaluated as the endpoint was considered not sensitive to the treatment. In study 102, the effects of lum/iva are not from baseline, as patients were already on lum monotherapy. So the additional contribution of ivacaftor on PD effects is not clear. Furthermore, the pivotal studies did not evaluate effects on sweat chloride and so evidence on long-term maintenance of target effects is also not available.

In the phase 2 clinical studies 101 and 102, reports of transient but significant drops in FEV1 due to an off-target effect of lumacaftor were observed and this was persistent for the observed treatment duration of 28 days. This effect did not result in significant withdrawals and could be managed by bronchodilators as this off-target effect was reported to be reversible. However, the applicant did not further evaluate the lumacaftor monotherapy based on the observed transient bronchoconstriction. The additional contribution of ivacaftor on FEV1 is therefore available only in short-term studies and not from long-term studies.

A treatment effect on the reduction in the slope of decline in FEV1 has not been conclusively demonstrated. An accrual of positive treatment effect with lum/iva cannot be inferred with confidence given the small effect size. A constant 2.55% difference in FEV1 through life may not justify using the combination as a life-long treatment, but an accrued benefit in FEV1 expanding with time from a 2% baseline can be significant and support a life-long therapy. The applicant has presented analyses from the additional data available from second interim analysis of study 105 which shows a trend towards reducing the slope of decline. Given the smaller than anticipated 'effect size' and the lack of conclusive evidence in altering the disease pathology beneficially, additional long-term data would be required post-authorisation. The effects on CFQ-R and BMI though supportive do not in themselves allow for conclusion of clinical relevance. The clinical relevance of the BMI changes in terms of lung function and overall patient benefit remains to be fully explored. The effects of lum/iva on pancreatic function have not been evaluated in detail.

Only interim data from study 105 is available for a total treatment duration of up to 48 weeks, although the study is planned to provide data from total treatment duration of up to 120 weeks. Data from this ongoing study is important in the context of the small effect size seen on the primary endpoint, the lack of adequate evaluation of lumacaftor monotherapy and the lack of adequate evidence for a clinically relevant contribution of ivacaftor over the long term. Upon CHMP's request, the applicant committed to provide this long-term data during the post-authorisation phase as agreed in the RMP.

Although the effects were demonstrated in a typical clinical study population, the representation of patients with rapidly progressive disease and patient with higher number of exacerbations could have been higher. Nevertheless, in the context of this rare disease this is considered acceptable for authorisation. Although two dose regimens were evaluated in the pivotal phase III studies, there was no statistical comparison between these two dose regimens which were close to each other. The difference in efficacy and safety between the two dose regimens is not conclusive. In this background, it is uncertain if the proposed LUM/IVA 400/250mg BD is preferable to LUM 600mg OD/IVA 250 mg BD.

Risks

Unfavourable effects

The main unfavourable adverse events related to treatment with lumacaftor/ivacaftor were respiratory (cough, dyspnoea and bronchospasm) and gastrointestinal (diarrhoea, nausea and vomiting). SAEs were reported in 28.6% of patients taking placebo and 20.1% of patients taking lumacaftor/ivacaftor. Few of these were thought to be related to study medication (placebo 2.2%, LUM/IVA 600qd/250q12h 2.2%, LUM/IVA 400q12h/250q12h 3.8%) of which the most commonly reported were increased creatinine phosphokinase, liver function test abnormal, bronchospasm and rash. Reports of increased liver transaminases are confounded by the fact that patients with CF are predisposed to liver abnormalities. However a causal relationship cannot be ruled out and warnings are included in the SmPC with advice to monitor LFTs before instigating therapy with lumacaftor/ivacaftor and at regular intervals during therapy.

Menstrual abnormalities occurred as well, particularly in patients taking the oral contraceptive pill (OCP), and are most likely due to induction of CYP3A enzymes by lumacaftor affecting the metabolism of the OCP. Therefore it is advised that non-hormonal contraception should be used when taking lumacaftor/ivacaftor, as per the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Raised hepatic enzymes have been reported in healthy volunteers and patients taking lumacaftor/ivacaftor and it are currently unknown whether this translates into hepatotoxicity with longer term therapy. Monitoring of liver function tests is recommended upon initiation and during treatment with lumacaftor/ivacaftor.

In addition, raised creatinine phosphokinase has been reported with a diagnosis of asymptomatic rhabdomyolysis in one healthy volunteer. The mechanism by which lumacaftor/ivacaftor leads to raised creatinine phosphokinase is not understood; neither is it known whether this could result in further cases of rhabdomyolysis with wider exposure to the drug. Following review of all cases of raised CPK in the clinical programme, out of eleven cases of raised CPK on active treatment who discontinued, seven had positive de-challenge returning back to baseline, and four had negative de-challenge with persistent elevated levels. Overall, apart from the imbalance in discontinuations, the absolute incidence of CPK was similar in active and placebo treatment arms. The applicant could not identify any biological mechanisms that could possibly result in raised CPK. Therefore, currently there seems to be not solid evidence to implicate lum/iva in raised CPK.

Ophthalmological effects have been reported in association with ivacaftor exposure in juvenile rats and an observational study in children under the age of 12 years is ongoing. In the Phase III placebo-controlled studies for lumacaftor/ivacaftor, subjects over the age of 12 years were enrolled and a baseline ophthalmological examination was performed to rule out pre-existing abnormalities but there are no plans for follow up examinations following long-term exposure in Study 105. The applicant was recommended to arrange for ophthalmological examinations of subjects leaving Study 105 wherever feasible. It is unknown whether the ophthalmological effects seen in juvenile rats have any relevance to treatment in humans. The concern is particularly in children under 12 years of age and it is proposed that treatment with lum/iva is limited to treatment of children and adults over the age of 12 years, which is hence reflected in the indication of Orkambi.

Further data on long term exposure to lumacaftor/ivacaftor were submitted from study 105. Approximately 683 patients received lumacaftor/ivacaftor for at least 48 weeks. There is no firm evidence that longer-term exposure to lumacaftor/ivacaftor leads to increased risks and the long term safety study is still ongoing. The applicant has committed to submit a final report on Study 105 and to endeavour to follow up the patients up to 5 years, as described in the section on Risk Management Plan.

Benefit-risk balance

Importance of favourable and unfavourable effects

Although the effect-size on the surrogate primary endpoint of change in ppFEV1 is small, a consistent effect has been demonstrated across the two studies and for the two dose-regimens of the lum/iva combination. Further the results on the other spirometry endpoints are similarly consistent and supportive of the observations on the primary endpoint. These observations are also supported by the results on other secondary endpoints of BMI and CFQ-R and although all observations were not significant, they were at least numerically in favour of the treatment arms.

In addition, relevant effects on clinical endpoints of a number of pulmonary exacerbations including those that require IV antibiotics and those requiring hospitalisation have been demonstrated. The effects on these endpoints appear consistent across both studies and for both the dose-regimens. A positive effect is seen on the gastrointestinal/nutritional endpoint as well suggesting correction of CFTR defects in an organ system other than lung. Moreover, these endpoints (FEV1, exacerbations, nutritional status) are co-related with mortality in CF.

However, in the CHMP's opinion, some uncertainties about the favourable effects of Orkambi remain. Solid supporting evidence from PD results which could provide evidence for additive and long-term effects on target-CFTR protein activity is not available. The small effect size on lung function would not be adequate to support a chronic life-long treatment of patients, especially when the responder analysis showed that more than 50% of the treated patients did not achieve a >5% improvement in ppFEV1. The effects on CFQ-R and BMI, though supportive, do not in themselves support a conclusion of major clinical relevance. However given the consistency in results across the endpoints in different subgroups and

across the three studies, it can be accepted that there is a clinically relevant and significant treatment effect which is maintained for the duration of 48 weeks treatment in line with the currently available data. The concern on whether the treatment will continue to be beneficial beyond that duration, especially as a conclusive effect in the alteration of disease pathology has not yet been demonstrated, can only be answered when further longer term data are available. It is acceptable for this data to be submitted in the post-authorisation phase.

Furthermore, the study population seems to be poorly represented with patients with higher degree of exacerbations and with patients who have rapidly progressive disease. The typical study population in a controlled study is limited in its ability to represent the true clinical population by the selection criteria. The real results of the treatment in the overall patient population will be seen in the post-authorisation setting; hence the applicant is requested to report the results of study 105 in a timely manner as reflected in the RMP.

Although the use of a free-combination offers more flexibility and permits dose-titration in general, based on the low number of treatment discontinuations in case of lum/iva, the real need for dose-titration is not apparent. Therefore, the fixed-dose combination which offers more convenience especially when it comes to compliance, can be accepted.

The LUM/IVA 400/250mg BD has not been associated with a significantly higher safety concerns than ivacaftor and has been consistently associated with at least a numerically higher effect on pulmonary exacerbations across the studies. Therefore the proposed LUM/IVA 400/250mg BD dose is acceptable to the CHMP.

Most of the unfavourable effects are related to the GI system or respiratory system and these have generally been mild to moderate. Serious adverse events have not been generally reported with a higher incidence than placebo. The only serious adverse reactions occurring in at least 0.5% of patients on Orkambi and greater than placebo were hepatobiliary events, including 4 reported as transaminase elevations, 2 as cholestatic hepatitis, and 1 as hepatic encephalopathy. There are safety concerns related to raised creatinine phosphokinase, raised liver enzymes and cataract formation, but the extent of clinical concern due to these signals has not yet been fully characterised. These events are being monitored and adequate information has been included in the SmPC and RMP of Orkambi to ensure their control.

Benefit-risk balance

A consistent and significant effect of lum/iva on the surrogate endpoint of change in ppFEV1 has been demonstrated. FEV1 is a known predictor of mortality in CF and is an accepted primary endpoint. The effects on secondary endpoints support the conclusions drawn based on the primary endpoint. Furthermore, a robust effect on clinical endpoints of pulmonary exacerbations, including exacerbations requiring IV antibiotics and exacerbations requiring hospitalisations, has been demonstrated. These results are supported by the observations in the longer term (48 weeks) data. The results in different sub-groups, based on baseline lung function, concomitant medication, age, rate of progression, early effects on lung function, appear to be in favour of the treatment. However, given the small effect size, longer term data (beyond 48 weeks) are considered necessary to be provided. The CHMP accepted this to be collected in the post-authorisation setting. Overall, the effect size on the primary endpoint is smaller than anticipated and similar to the effect of other symptomatic treatments, which is sub-standard for a treatment that targets disease pathology especially in light of the expectations set by ivacaftor therapy in CFTR G551D. However it is acknowledged that CFTR F508del is a more severe condition and moreover the effect size is an added benefit on top of standard of care where this target group have no other alternative treatment options. In this context, the observed effects on the primary endpoint can be considered clinically relevant. The overall treatment effects remain clinically meaningful till 48 weeks and the available evidence on efficacy is considered adequate to support the proposed use of LUM/IVA.

The adverse events of the combination have generally been associated with GI and respiratory system and have been mild to moderate. The combination does not increase the incidence of severe adverse events except a small rise in hepatobiliary events as compared to placebo. It is agreed that the combination of lum/iva has an acceptable safety profile at the proposed dose in the target population.

Discussion on the benefit-risk balance

Similar benefit of lum/iva combination has been demonstrated with both the dose-regimens tested in both studies. The effect-size and the direction of the effects on all the evaluated endpoints are comparable between the two studies. So it can be accepted that the treatment benefits seen in the two studies (study 103 and study 104) are a realistic estimation of the treatment effects of lum/iva. The extent of benefit is smaller than anticipated as seen by the effect-size on the primary endpoint of change in FEV1. The seen effect is smaller than the anticipated benefit and smaller than the effect seen with ivacaftor in CF patients with G551D defect. However, it should be considered that this effect is over and above the current concomitant treatment. In this context an added treatment effect albeit one that is comparable to other symptomatic treatments is clinically relevant. Furthermore, the effect on pulmonary exacerbations and other endpoints is more robust and in itself the effect size demonstrated in the reduction in number of pulmonary of exacerbations including those requiring IV antibiotic therapy and those requiring hospitalization is considered clinically relevant. The effects on CFQ-R and BMI are not conclusive of a clinically relevant treatment effect in themselves. The observed clinical relevance of a constant 2.5% improvement on lung function up to 48 weeks of treatment is expected to be further supported by the evidence on maintenance of treatment effects beyond 48 weeks in the post-authorisation setting.

The long-term data of treatment up to 48 weeks showed the maintenance of effect on exacerbations in the patients who had received active treatment in the pivotal studies. In patients who received placebo in the pivotal studies, and were crossed over to active treatment, beneficial effect on all endpoints including exacerbations was noted which was of a comparable magnitude to the effect seen in the active treatment arms during the pivotal studies. There are certain sub-groups like patients with rapid progression and patients with high number of exacerbations/year that appear to be under-represented in the study population. Results from such patients are expected from the post-marketing setting data.

The proposed dose has been evaluated in a reasonable number of patients for up to 48 weeks treatment. The combination has been generally well tolerated with very few discontinuations through-out the 48 week study period. The main adverse events related to treatment with lumacaftor/ivacaftor were respiratory (cough, dyspnoea and bronchospasm) and gastrointestinal (diarrhoea, nausea and vomiting) which were generally mild to moderate. The incidence of serious adverse events was lower in active treatment as compared to placebo. The common related serious adverse reactions included increased creatinine phosphokinase, liver function test abnormal, bronchospasm and rash. Overall the safety profile of the combination has been reasonably well characterised. The observed risks are generally mild to moderate. The potential significant risks can be monitored in the clinics and can be adequately addressed in the RMP.

Given that adequate evidence of a clinical relevant efficacy maintained over 48 weeks treatment has been demonstrated and the characterised safety profile shows the combination has acceptable tolerability, the benefit-risk analysis is considered positive. The long-term safety and efficacy of Orkambi will be monitored in a post-marketing setting.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Orkambi is not similar to Bronchitol and Kalydeco within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Orkambi in the treatment of
Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene (see sections 4.4 and 5.1).
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance lumacaftor, contained in Orkambi, the CHMP considers that lumacaftor is qualified as a new active substance. (see Appendix 2)