9 November 2017
EMA/781319/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Orkambi

International non-proprietary name: lumacaftor / ivacaftor

Procedure No. EMEA/H/C/003954/X/0020

Note

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

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List of abbreviations

CQA Critical Quality Attribute
DMR Desired Manufacturing Ranges
DoE Design of experiments
DSL Design Space Limits
FDC Fixed dose combination
HPLC High performance liquid chromatography
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IG Intragranular
IR Infrared
KF Karl Fischer titration
NOR Normal Operating Range
PCTFE Polychlorotrifluoroethylene
Ph. Eur. European Pharmacopoeia
PVC Poly vinyl chloride
QbD Quality by design
RH Relative Humidity
SDD Spray-Dried Dispersion drug product intermediate
SmPC Summary of Product Characteristics
TAMC Total Aerobic Microbial Count
TSE Transmissible Spongiform Encephalopathy
TSWG Twin-Screw Wet Granulation
TYMC Total Combined Yeasts/Moulds Count
XR(P)D X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Europe) Ltd. submitted on 3 March 2017 an extension of the marketing authorisation to add a new strength of film-coated tablets (100 mg Lumacaftor / 125 mg Ivacaftor) for paediatric use (6 to 11 years). The RMP (version 3.1) is updated accordingly.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Orkambi, was designated as an orphan medicinal product EU/3/14/1333 on 20 September 2010 in the following condition: treatment of cystic fibrosis. The MAH has withdrawn the Orphan Designation on 09-10-2015 and therefore this product is no longer an orphan medicine. The new indication, which is the subject of this application, does not fall within any orphan designation.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0220/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0220/2016 was 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 MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Additional Data exclusivity / Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

Protocol Assistance

The MAH received Protocol Assistance from the CHMP on 26 February 2015. The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP:

Rapporteur: Nithyanandan Nagercoil

CHMP Peer reviewer: N/A

- The application was received by the EMA on 3 March 2017.
- The procedure started on 23 March 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 June 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 21 June 2017.
- During the meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 20 July 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 11 September 2017.
- In cases when a pre-authorisation inspection has been conducted, please reflect the following steps (include/delete information as applicable):
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 11 October 2017.
- During the PRAC meeting on 23-26 October 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 9 November 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Orkambi.
- The CHMP adopted a report on similarity of Orkambi (lumacaftor/ivacaftor) with Bronchitol (mannitol), Cayston (aztreonam), TOBI Podhaler (tobramycin) and Kalydeco (ivacaftor) on 9 November 2017 (Appendix 1).
- The CHMP adopted a report on the significant clinical benefit for Orkambi in comparison with existing therapies (Appendix 2).

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cystic fibrosis (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. 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 (class II).

2.1.2. Epidemiology

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. The median predicted age of survival for patients with CF born in 2014 is 40.0 years of age. 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. Although expected survival has doubled over the past 30 years due to advances in treatment, of those who died in 2014, the median age at death ranged from 27.0 to 32.4 years in the US, Canada, EU, and Australia.

Orkambi is approved in the EU for the treatment of CF patients 12 years and older who are homozygous for the mutation F508del, the commonest disease-causing CFTR mutation. In the EU, approximately 80% of patients with CF have F508del on at least one allele and 40% are homozygous for F508del.

2.1.3. Clinical presentation, diagnosis

The biochemical defect of defective chloride channel function is present from birth, with the sequelae of lung, pancreatic and other organ involvement emerging progressively throughout childhood and into adulthood.

The indication is restricted to the homozygous F508del-CFTR genotypic subpopulation of CF who have a severe form of the disease due to the very low level of chloride channel function. Even in this severely affected subgroup, however, lung injury proceeds at a slow rate and pulmonary function as measured by spirometry can be apparently normal in the 6 – 11 year old age group. Nonetheless, even with normal spirometry, patients can have pulmonary structural aberrations on computed tomography (CT) scans. Consistent with this, impaired lung clearance index (LCI), which measures the degree of small airway disease by assessing ventilation inhomogeneity, can be demonstrated in paediatric patients with normal spirometry. Because the underlying molecular defect is the same in this age group and older patients, it was anticipated that LUM/IVA may be efficacious in this population to slow or pre-empt disease progression by correcting the biochemical defect in the chloride channel protein.

2.1.4. Management

Lumacaftor is a CFTR corrector and IVA 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.

A modest restoration of chloride secretion through the action of the combination of LUM and IVA in vitro has been shown to improve fluid regulation and ciliary beat frequency in primary cultures of human bronchial epithelial (HBE) cells derived from donors with CF who are homozygous for the F508del-CFTR mutation. In individuals with CF, this would be expected to improve the mucociliary clearance to alleviate the cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs, and eventually respiratory failure for patients with CF.

Lumacaftor and ivacaftor target the biochemical defect in the chloride channel protein whereas all other current treatments for CF alleviate the clinical manifestations of the disease but do not act on the underlying chloride channel defect. Current treatments include inhaled mucolytics, bronchodilators, antibiotics, anti-inflammatory medicines, and pancreatic enzymes.

About the product

Orkambi is a fixed drug combination of lumacaftor and ivacaftor that combines corrector and potentiator action to provide a partial reversal of the biochemical defect in the chloride channel due to mutation in the CFTR gene.

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).

The extended indication will be: Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene (see sections 4.2, 4.4 and 5.1).

Ivacaftor is a potentiator of the CF transmembrane conductance regulator through increased gating activity, resulting in increased chloride transport. F508del-CFTR is a Class II mutation leading to an aberrantly folded protein susceptible to defective intracellular processing and trafficking that prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. The very small amount of F508del-CFTR protein that reaches the cell surface also has defective channel gating and decreased stability at the cell surface. Patients who are homozygous for F508del-CFTR have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease. Lumacaftor is presumed to partially correct the folding defect in F508del-CFTR, facilitating its cellular processing and trafficking, allowing the protein to reach the cell surface. 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 in vitro to F508del/F508del human bronchial epithelial cells (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.

Type of Application and aspects on development

The line extension application is for an extension of indication to children 6 years and older, from the currently approved target population 12 years and older. The same genotypic subpopulation of cystic fibrosis (homozygous for the F508del mutation in the CFTR gene) is indicated. Orkambi is authorised in the EU as a single strength LUM 200-mg/IVA 125-mg FDC tablet for oral administration, given as 2 tablets (administered dose LUM 400 mg/IVA 250 mg) every 12 hours. The line extension proposes an additional lower strength FDC tablet, with a different ratio of LUM to IVA (LUM 100-mg/IVA 125-mg) from the existing strength (LUM 200-mg/IVA 125-mg) to be administered as 2 tablets every 12 hours in CF patients 6 to 11 years of age with the F508del CF mutation. The total daily administered dose of LUM is therefore half (400 mg) that of the daily dose in children 12 years and older (800 mg) whereas the daily dose of IVA is the same (500 mg) in both age groups.

This line extension is supported by a new combination of Orkambi with an altered ratio of LUM:IVA (50% reduction in LUM while maintaining the same quantity of IVA) intended for the 6 -11 years age group. The altered ratio was informed by PK modelling and supported by new PK data in the 6 -11 year old CF patients together with Population PK analysis comparing LUM and IVA exposures in 6-11 year olds compared with patients 12 years and older. The line extension dossier provides a single confirmatory efficacy and safety study of the age appropriate formulation at the proposed posology in the extended target population.

2.2. Quality aspects

2.2.1. Introduction

This application concerns a line extension of the currently authorised Orkambi 200 mg/125 mg film-coated tablets to introduce an additional strength for the treatment of patients from 6 to 11 years of age.

The finished product is presented as fixed dose combination (FDC) film-coating tablets for oral administration containing 100 mg of lumacaftor and 125 mg of ivacaftor as active substances.

Other ingredients are:

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

Tablet 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 polychlorotrifluoroethylene (PCTFE)/ Polyvinyl chloride (PVC) with a paper-backed aluminium foil lidding, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substances lumacaftor and ivacaftor have already been approved as active substances in Orkambi 200 mg/125 mg film-coated tablets of the same applicant. No new information on the active substances has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The proposed new strength is also a fixed dose combination (FDC) presented as pink immediate-release film-coated tablets for oral administration containing 100 mg of lumacaftor and 125 mg of ivacaftor as active substances. The tablets are printed in black ink with “1V125” on one face.

Similar to the existing strength, lumacaftor active substance is provided as a crystalline solid and ivacaftor active substance is provided as an amorphous spray dried dispersion (SDD) intermediate. The composition of this strength is very similar to the marketed 200 mg/125mg tablets in terms of the content %. he excipients used are qualitatively the same as those contained in the existing 200mg/125 mg FDC tablets. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Product and manufacturing process development were conducted under a Quality by Design (QbD) paradigm. Much of the information presented for the registration of the 100mg/125 mg FDC tablets is common to the previously approved 200mg/125 mg FDC tablets. The components of the finished products, formulation development and manufacturing process development are identical for both strengths.

The critical quality attributes (CQAs) and criticality thresholds of the 100mg/125 mg FDC tablets are the same as for the 200mg/125 mg FDC tablets. The proposed changes to the dossier relating to the 100mg/125mg tablet have been provided. The main changes are with regards to the continuous manufacturing process development. In this regard, the desired manufacturing ranges (DMR) for the process parameters evaluated are also identical to those of the 200mg/125mg tablets with the exception of water added during twin-screw wet granulation (TSWG), intragranular (IG) blend fill level, and compression force, where some adjustments were made due to the changes in formulation.

QbD experiments were executed across all steps in the manufacturing process to evaluate the impact of material attributes and process parameters on the drug product CQAs. The experimental designs of the IG blending and compression processes were equivalent to those of the 200/125 mg FDC tablet. A DOE for TSWG through milling and another DOE for compression were conducted, which led to the establishment of design spaces. No DOE was executed for the film-coating step, since the core tablet thickness of the 100/125 mg FDC tablet is within the range previously studied during 200mg/125 mg and 200/83 mg FDC tablet development and therefore the criticalities and design space limits established for them are applicable to the 100mg/125 mg FDC. However, a single coating experiment at the wettest condition was conducted to confirm that there was no impact of coating parameters on physical form. Design spaces were established for IG blending, continuous manufacturing steps (granulation though compression) and film-coating.

Finally, confirmatory runs were completed in order to validate predictive models for dissolution developed throughout previous QbD experiments in addition to verifying processability throughout the DMR at the planned commercial site. All dissolution values were within specification and acceptability with regard to magnitude/directionality of effect of the statistically significant process parameters and material attributes was confirmed.

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 commercial manufacturing process for the 100mg/125 mg lumacaftor/ivacaftor FDC tablet is very similar to the existing 200mg/125mg tablets, with some adjustments on some operating ranges as described under the manufacturing process development section above.

Briefly, the manufacture of Orkambi FDC tablets is a two-stage process.

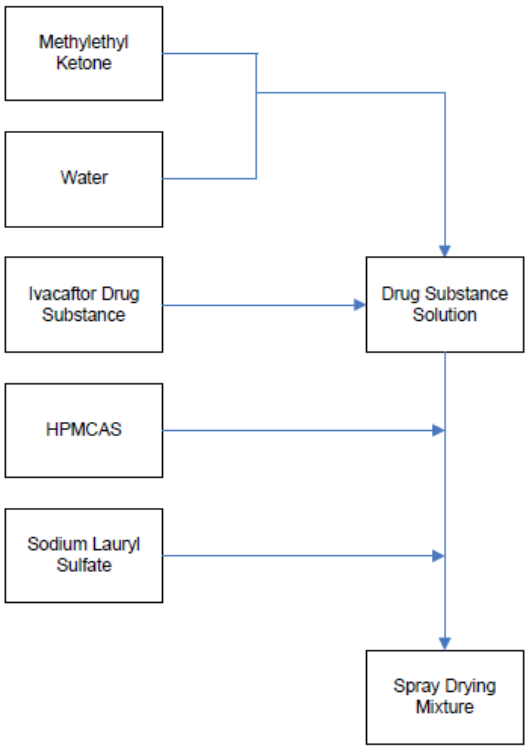
In the first stage (figure 1), crystalline ivacaftor active substance is dissolved with a polymer and a surfactant in the process solvents, then spray dried to form a powder, which undergoes secondary drying

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.

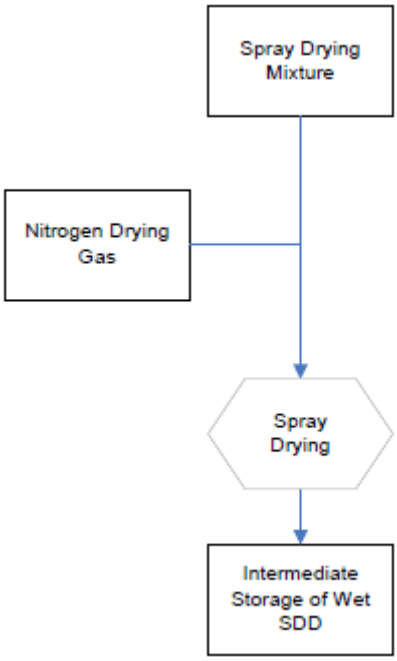
The second stage, which involves the manufacture of the FDC tablets, consists of seven steps: intra-granular blending of ivacaftor SDD and lumacaftor, twin screw wet granulation, fluid bed drying and milling, extra-granular blending, compression, film coating, and printing.

The process flow diagram for the second stage is shown in figure 2, with the blue box denoting the portion of the manufacturing process that is operated on a continuous mode (all steps granulation to compression). Intragranular blending and film coating are performed in batch mode.

Step 1. Mixture preparation



Step 2. Spray drying



Step 3. Secondary drying

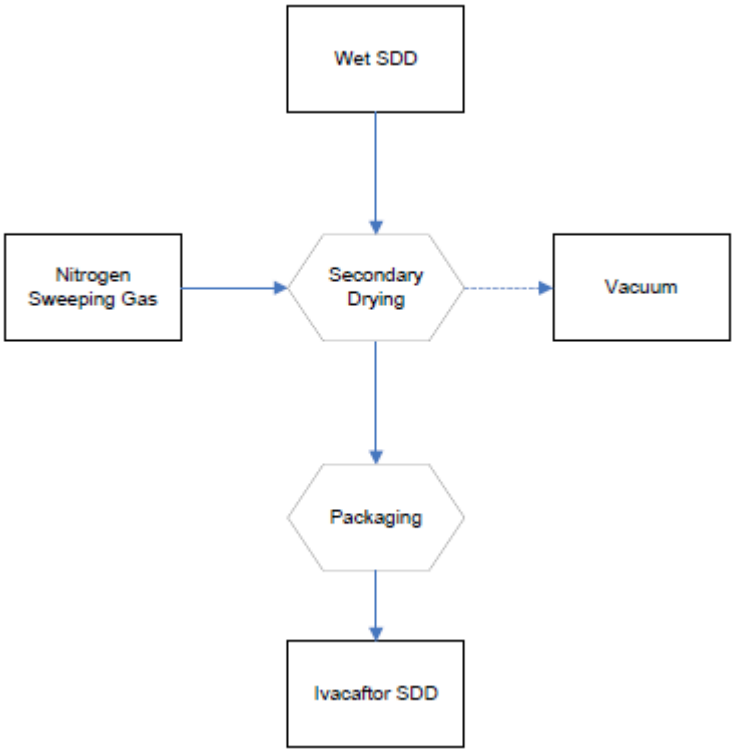


Figure 1. Process flow diagram for ivacaftor SDD.

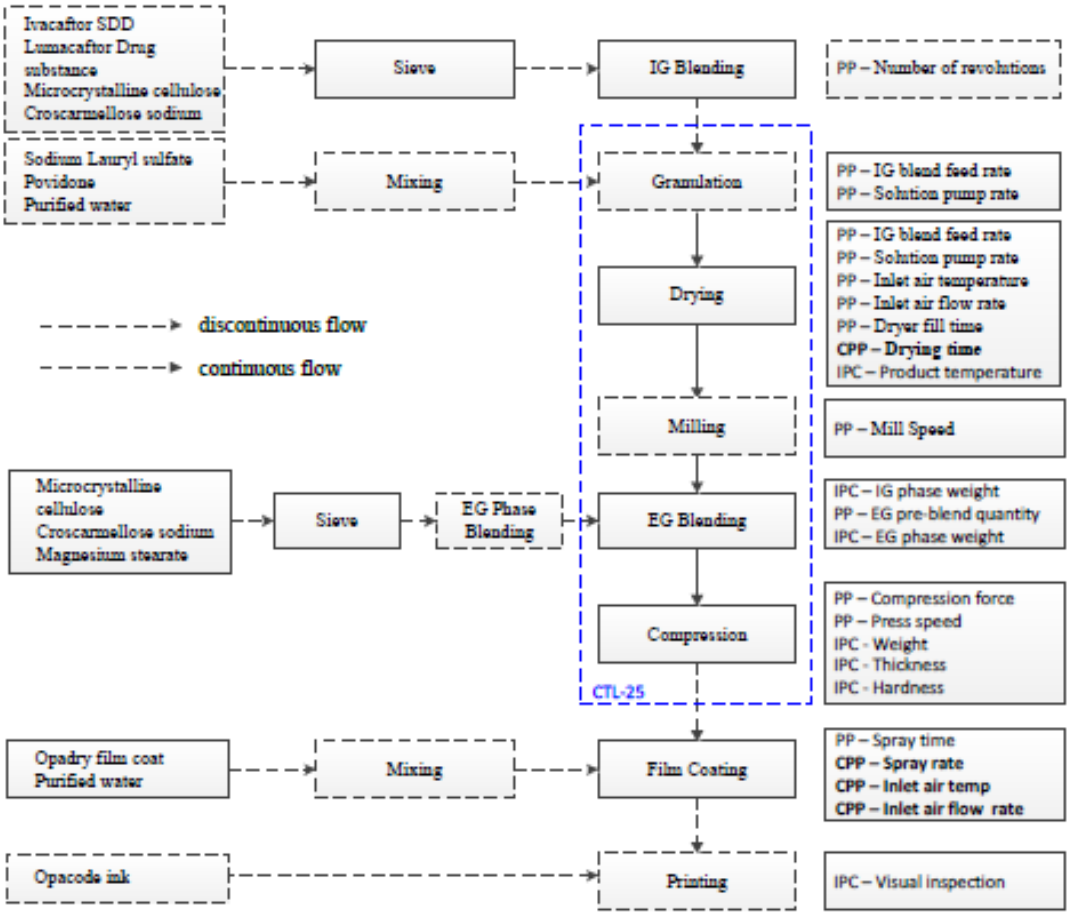


Figure 2. Process flow diagram for Lumacaftor/Ivacaftor 100mg/125mg FDC tablets (second stage). The dashed boxes indicate the boundaries of the continuous process equipment used at the proposed manufacturing site.

As indicated above, design spaces have been defined for IG blending, continuous manufacturing steps (granulation though compression) and film-coating. Adequate in-process controls have been defined.

Design spaces have been established for the several steps of the manufacturing process of the SDD (spray drying) and the FDC tablets: intra-granular blending, twin screw wet granulation, fluid bed drying and milling, extra-granular blending, compression and film coating. The desired manufacturing ranges (DMR) for the process parameters evaluated are also identical to those of the 200mg/125mg tablets with the exception of water added during TSWG, IG blend fill level, and compression force. There are a number of process parameters that have differing design space limits (DSL) and normal operating range (NOR) set points when compared to the approved 200mg/125mg tablets. Satisfactory justification for those changes was provided during the evaluation and it was concluded that the proposed DSL ranges for the 100 mg/125mg tablets are acceptable. As for the 200mg/125mg tablets, design spaces have been developed at the commercial scale manufacturing equipment.

Process validation of the ivacaftor SDD intermediate manufacturing process was performed for the registration of the 200mg/125mg tablets on three 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), was conducted on three consecutive commercial scale batches at the proposed manufacturing site (in line with the submitted process validation scheme. It has been demonstrated that the process is capable of reproducible commercial manufacture.

Product specification

The product release specification is based on the 200mg/125mg tablet with the proportional reduction in strength. The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (IR), assay (HPLC), dissolution (Ph. Eur.), water content (KF), uniformity of dosage units (HPLC) and physical form of lumacaftor and ivacaftor (XRPD).

The finished product is released on the market based on the above release specifications, through traditional final product release testing,

The description and appearance of the lumacaftor/ivacaftor FDC tablet, 100mg/125 mg as pink film-coated tablet, printed in black ink with “1V125” on one face is similar to the 200mg/125 mg tablet. During the evaluation there were concerns that the different strengths would not be sufficiently distinguishable. The applicant stated in his response, that the 100/125mg tablet and the 200mg/125mg tablet can be distinguished by three factors: print, shape and size/thickness. In addition, the commercial packaging of the two FDCs are clearly labelled and can be easily distinguished. Although there is a potential for confusion with regards to the print on the tablets (where only 1 figure is different out of 5 figures), it was concluded that there are sufficient distinguishing factors such as size/thickness and colour in the outer packaging is clearly distinguishable and the applicant’s proposal was considered acceptable.

Lumacaftor and ivacaftor are both stable molecules. No degradation products were observed at or above the reporting threshold (0.10% w/w) in representative lots of lumacaftor/ivacaftor FDC tablets at release or on stability. In addition, no degradation products were seen during development or during QbD studies. Therefore degradation products are not included in the release specification and are tested on stability only.

The analytical methods used are identical to those already approved for the 200mg/125mg tablets. They have been adequately described and appropriately validated in accordance with the ICH guidelines. The information regarding the reference standards used for assay is the same as that presented for the approved 200mg/100mg tablets.

Batch analysis results are provided for four batches used in clinical studies and formal stability studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three formal stability batches of finished product stored under long term (25 ºC / 60% RH) or intermediate (30 °C ± 2 °C/65% RH ± 5% RH) conditions for 24 months and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of Orkambi 100mg/125mg tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples stored at long term and accelerated conditions were tested for appearance, assay, degradation products (validated HPLC), dissolution, ivacaftor and lumacaftor physical form. Samples stored at intermediate conditions were tested for microbial count (TAMC, TYMC) and specified microorganisms: *E. coli*. The analytical procedures used are stability indicating.

All results met the acceptance criteria for the attributes evaluated and no trends were observed for assay or degradation products. Although a slight downward trend was observed in ivacaftor dissolution at 25°C/60% RH and lumacaftor dissolution at 40°C/75% RH, all results remained within the acceptance limits and are expected to remain within those limits through the proposed shelf-life period.

Although water content is not a formal stability test, it was monitored throughout stability. Although a small increase in water content was observed under the long-term and accelerated storage conditions, it has no impact on the tablet physical and chemical properties.

In addition, photostability per ICH Q1B, Option 2, was evaluated on one batch of lumacaftor/ivacaftor 200mg/125mg tablets. 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.

Overall, the stability data presented is in line with the results observed on the approved 200mg/125 mg tablets. They showed that the finished product is chemically and physically stable when packaged in the configuration proposed for commercial distribution under all storage conditions.

Based on available stability data, the proposed shelf-life of 36 months with the storage recommendation to store below 30°C as stated in the SmPC (section 6.3) is 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 100mg/125mg FDC tablets has been presented in a satisfactory manner.

The applicant has applied the same QbD principles used for the existing 200 mg/125 mg FDC tablets for the development of this new strength. Design spaces have been proposed for several steps in the manufacture of the finished product. The design spaces have been adequately verified.

The manufacture of the FDC tablets uses a continuous wet granulation process. Drying, milling, extragranular blending and compression are also performed in a continuous mode.

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.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

For the current extension of indication to children 6-11 years old, no nonclinical data on pharmacology, pharmacokinetics and toxicology were provided, apart from lumacaftor juvenile toxicity study conclusions (see section 2.3.4).

Previous reproductive, developmental and embryo-foetal development toxicity studies conducted with lumacaftor in rats and rabbits indicated that it is not a reproductive and/or developmental toxicant and not teratogenic or a developmental toxicant in rats and rabbits. When co-administered to rats, lumacaftor and its metabolite M28-lumacaftor, did not result in toxicity to male or female reproductive systems and did not produce any adverse effects on maternal and/or F1-generation prenatal/postnatal development. M28-lumacaftor produced developmental toxicities (foetal malformations) only at high doses which resulted in significant maternal toxicity in rats.

The reproductive and developmental toxicity profile of ivacaftor, together with the assessment of juvenile toxicity has previously established in rats and rabbits in support of the registration of KalydecoTM. Ivacaftor had minimal effects on female reproduction and foetal development in rats, which were attributed to significant maternal toxicity, and it was associated with ocular toxicities in juvenile animals. Ivacaftor was not teratogenic in rats and rabbits and had no effects on the male rat reproductive system, but had effects on female rat reproduction (54% reduction in fertility index and number of pregnancies/cohabiting female) and on early embryonic development (increases in pre- and post-implantation loss and litters consisting of all nonviable embryos and changes in estrous cycling) at maternally toxic doses. There were no adverse effects on learning and memory or on reproductive capacity in offspring (F1 generation rats). Juvenile toxicity studies identified the eye (lens opacities/cataracts) as a target organ of toxicity, which were not detected in repeat-dose toxicity studies conducted in older mice, rats, or dogs.

2.3.2. Pharmacology

No nonclinical studies were conducted as the pharmacology of ivacaftor and lunacaftor is well known.

2.3.3. Pharmacokinetics

No nonclinical studies were conducted as the pharmacokinetics of ivacaftor and lunacaftor is well known.

2.3.4. Toxicology

In the juvenile rat study, lumacaftor at 500 mg/kg/day was associated with mortality in one male animal on PND 10. Macroscopic and microscopic were suggestive of postnatal hypoglycaemia which may have been associated with a failure of suckling. No other target organ toxicity was observed at 125 and 250 mg/kg/day and therefore the dose of 250 mg/kg/day is deemed to be the NOAEL. The exposure to lumacaftor observed at this dose represents an approximate 5-fold safety factor to that seen in subjects aged 6 to 11 years in clinical study 011.

2.3.5. Ecotoxicity/environmental risk assessment

A definitive assessment on the potential risk of ivacaftor and lumacaftor to the environment is not being made at this time but will be conducted once data from ongoing studies are submitted. The MAH has made a commitment to perform the required studies and update the ERA.

2.3.6. Discussion on non-clinical aspects

The results of the juvenile toxicity study do not affect the overall conclusions on the potential toxicity of lumacaftor and therefore no amendments to the SmPC are required and none have been made.

2.3.7. Conclusion on the non-clinical aspects

No issues have been identified from a nonclinical perspective and the lumacaftor juvenile data suitably supports this application for extension of Orkambi's use to children 6-11 years old.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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

Study 011

Phase 1 (Part A) and Phase 3 (Part B) Part A and B: PK (pediatric), safety, and tolerability Part B only: PD	VX13-809-011 (Module 5.3.3.2)	**Part A** Primary Objective Evaluate PK of multiple doses of LUM in combination with IVA Secondary Objectives • Investigate PK of a LUM metabolite, M28-LUM, and IVA metabolites, M1-IVA and M6-IVA • Evaluate safety and tolerability of multiple doses of LUM in combination with IVA **Part B** Primary Objective Evaluate safety and tolerability of LUM in combination with IVA through Week 24 Secondary Objectives • Evaluate the PD of LUM in combination with IVA through Week 24 • Evaluate off-drug response after the Washout Period (Week 24 to Week 26) • Evaluate PK of LUM, M28-LUM, IVA, M1-IVA and M6-IVA for LUM in combination with IVA	Open-label, 2-part, multiple-cohort, multiple-dose, multicenter	**Part A** **LUM/IVA (fixed-dose, film-coated):** 200-mg LUM/125-mg IVA tablet **IVA (film-coated):** 125-mg tablet LUM 200 mg q12h/IVA 250 mg q12h oral administration **Part B** **LUM/IVA (fixed-dose, film-coated):** 100-mg LUM/125-mg IVA tablet LUM 200 mg q12h/IVA 250 mg q12h oral administration	68 subjects total **Part A:** 10 subjects **Part B:** 58 subjects Male and female subjects aged 6 through 11 years (inclusive) with CF who are homozygous for the *F508del-CFTR* mutation	**Part A** 14 days **Part B** Approximately 24 weeks	Completed; Full

Study 109

Study Identifier	Study Design and Type of Control	Study Centers	Key Inclusion Criteria	Treatment	Number of Subjects Dosed/ Completed Treatment/ Completed Study	Duration of Treatment	Primary and Secondary Efficacy Endpoints[a]
Study 109	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	54 sites in North America, Europe, and Australia	• Confirmed diagnosis of CF • Homozygous for *F508del* • 6 through 11 years of age	LUM 200 mg/ IVA 250 mg q12h	204[b]/193/196	24 weeks	Primary Absolute change in $LCI_{2.5}$ from baseline through Week 24 Key Secondary • Average absolute change in sweat chloride from baseline at Day 15 and at Week 4 • Absolute change in BMI from baseline at Week 24 • Absolute change in CFQ-R respiratory domain score from baseline through Week 24 Other Secondary • Absolute change in $LCI_{5.0}$ from baseline through Week 24 • Absolute change in sweat chloride from baseline at Week 24 • Absolute change in $ppFEV_1$ from baseline through Week 24 • Relative change in $ppFEV_1$ from baseline through Week 24 • Absolute change in BMI-for-age z-score from baseline at Week 24 • Absolute change in weight from baseline at Week 24 • Absolute change in weight-for-age z-score from baseline at Week 24 • Absolute change in height from baseline at Week 24 • Absolute change in height-for-age z-score from baseline at Week 24 • Absolute change in TSQM domains from baseline through Week 24 • Time-to-first PEx through Week 24 • Event of having at least 1 PEx through Week 24 • Number of PExs through Week 24

Source: Module 5.3.5.1/VX14-809-109

BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FE-1: fecal elastase-1; IVA: ivacaftor; IRT: immunoreactive trypsinogen; LCI: lung clearance index; LUM: lumacaftor; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; TSQM: Treatment Satisfaction Questionnaire for Medication

[a] Other efficacy endpoints were absolute change in FE-1 levels from baseline at Week 24, absolute change in serum levels of IRT from baseline through Week 24, and absolute change in sputum microbiology from baseline at Week 24.

[b] There were 19 subjects who participated in the exploratory Imaging Substudy.

The pharmacokinetics data to support the dose selection for the pivotal efficacy and safety study 109 in the 6 – 11 years age group were derived principally from study 011, Parts A and B (Part A being a Phase I study that evaluated PK, safety and tolerability as a PK lead-in to Study 011B, a Phase III study that evaluated PK, PD, safety and tolerability). Study 109 was a Phase III, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of LUM/IVA for 24 weeks in subjects 6 through 11 years of age with CF, homozygous for F508del. Approximately 200 subjects were planned to be randomized (1:1) to LUM/IVA or placebo. Evaluation of PK was included as a secondary objective. Population PK models for LUM and IVA were utilized for evaluation of PK results obtained in Study 109. The objective of the population PK analysis was to characterize LUM and IVA exposures in subjects 6 through 11 years of age for comparison with exposures from subjects 12 years and older.

2.4.2. Pharmacokinetics

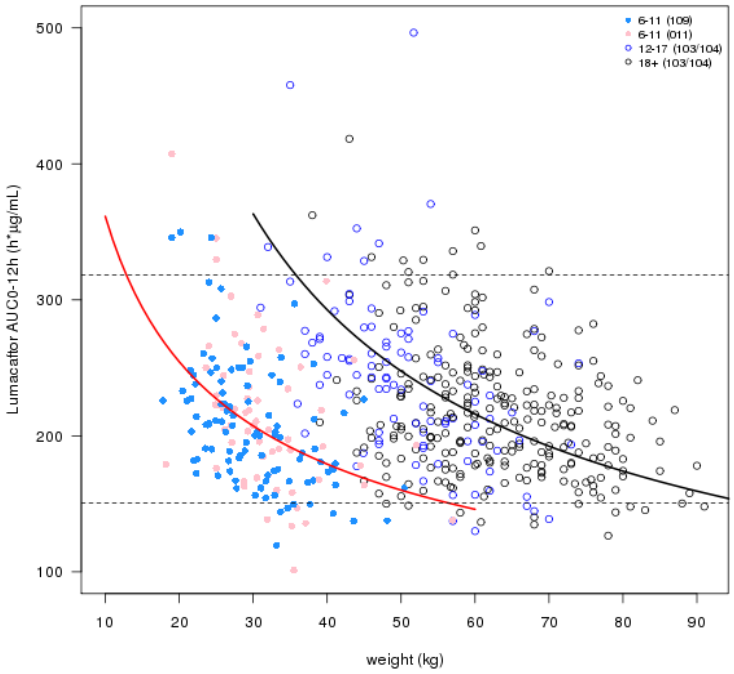
Orkambi is already authorised in the EU as a single strength LUM 200-mg/IVA 125-mg tablet for oral administration, given as 2 tablets (administered dose LUM 400 mg/IVA 250 mg) every 12 hours. This line extension includes an additional lower strength fixed dose combination tablet, with a different ratio of LUM to IVA (LUM 100-mg/IVA 125-mg) from the existing strength (LUM 200-mg/IVA 125-mg) to be administered as 2 tablets every 12 hours in CF patients 6 to 11 years of age with the F508del CF mutation. The total daily administered dose of LUM is therefore half (400 mg) that of the daily dose in children 12 years and older (800 mg) whereas the daily dose of IVA is the same (500 mg) in both age groups.

Pharmacokinetics (PK) modelling conformed the altered ratio of LUM:IVA in the new strength tablet (50% reduction in LUM while maintaining the same quantity of IVA) intended for the younger age group. Although decreased IVA clearance would be anticipated with decreasing body weight, this is offset by an increase in IVA clearance due to increased CYP3A4 induction from increased LUM exposure with decreasing body weight. Given that IVA is a CYP3A4 substrate, this will tend to reduce IVA exposure in patients with lower body weight. This is the essential basis for maintaining the IVA dose at the same level in the two tablet strengths.

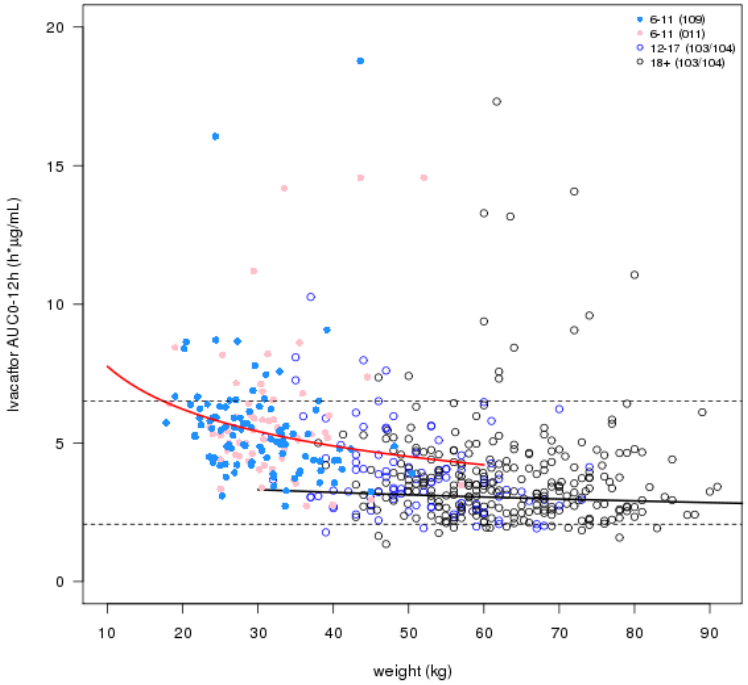
Pharmacokinetic data to support the line extension are mainly derived from two Phase III studies (study 011 B, an open label uncontrolled 24 week study; and study 109, a placebo controlled 24 week pivotal efficacy and safety study) together with a population PK analysis the objective of which was to compare observed, and predict population, data for LUM and IVA exposures in 6 to 11 year old patients compared with patients 12 years and older. In both 011B and 109, LUM/IVA were conducted in 6 – 11 year old CF patients homozygous for F508del-CFTR, the genotypic subgroup for which Orkambi is currently authorised, administered with the LUM/IVA FDC at the proposed posology for this age group. Both PK studies were conducted in the fed state, due to the increase in bioavailability of Orkambi with food, as recommended in the SmPC. Study 011B demonstrated that mean IVA and LUM concentrations in subjects 6 through 11 years of age were similar to those of subjects 12 years and older, administered with the respective age appropriate formulations. Population PK analysis (report Pop PK M406) was conducted on data from studies 109 and 011B (6 – 11 years age group) and compared to data from Studies 103 and 104 (age 12 years and above). All subjects were homozygous for F508del-CFTR and were administered with the respective formulations intended for their age group. The PK data set consisted of 918 lumacaftor and 907 ivacaftor plasma concentration measurements from 165 subjects over a 24-week period. There were slightly more female than male subjects. The age distribution was skewed towards older subjects. Weight ranged from 18 to 57 kg, with a median of 30 kg, see figure below.

Figure: LUM and IVA Exposures (AUC0-12h) Versus Weight for Subjects Given Age-Appropriate Doses of LUM and IVA

A. LUM



B. IVA



AUC: area under the concentration versus time curve; AUC_{0-12h}: area under the concentration versus time curve from the time of dosing to 12 hours; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetics; q12h: every 12 hours

Notes: PK data were taken from subjects 6 through 11 years of age in Studies 109 and 011B who received LUM 200 mg/IVA 250 mg q12h for 24 weeks (Study 109: solid blue circles; Study 011: solid red circles) and from subjects 12 years and older in Studies 103 and 104 who received LUM 400 mg/IVA 250 mg q12h for 24 weeks (subjects 12 through 17 years of age: blue circles; subjects 18 years and older: black circles). Dashed lines indicate 5^{th} and 95^{th} percentiles from Studies 103 and 104. Black and red curves are population predicted AUCs.

Population PK analysis showed that plasma concentrations of lumacaftor and ivacaftor in 165 CF subjects 6 to 11 years of age, who were treated twice daily for 24 weeks with lumacaftor in combination with ivacaftor, were well described by standard two-compartment PK models. The ivacaftor model was coupled to the lumacaftor model by a term that captures the induction of CYP3A by lumacaftor. This exposure-dependent induction of CYP3A increases ivacaftor's clearance. Model parameter estimates were similar to estimates that had been obtained previously for CF subjects 12 years and older.

The Pop PK data confirm the importance of body weight to lumacaftor and ivacaftor exposure and support the reduction in lumacaftor dose, while maintaining the same ivacaftor dose, in the younger age group. The majority of patients in the 6-11 years age group had LUM and IVA exposure levels that were within the 5th and 95th percentiles for LUM and IVA exposure in the older age group (12 years and above) administered with twice the dose of lumacaftor but the same dose of ivacaftor as in children 6 – 11 years. There was, as expected, a downwards trend to lower LUM exposure with increasing body weight in the 6 – 11 years age group. However, there was no clear relationship to body weight in the 6 – 11 years age group in those below the 5th percentile of LUM exposure. As for LUM exposure, the majority of IVA exposure in the 6 – 11 years age group is between the 5th and 95th percentiles for IVA exposure in the 12 years and above age group administered the age-appropriate formulation. In this case however, all the outliers in the 6 – 11 years age group were above the 95th percentile, some substantively so, suggesting that in some children, the higher ratio of IVA/LUM has over-compensated for the anticipated increase in CYP3A4 induction due to higher LUM exposure with decreasing body weight. As for the LUM outliers there was no clear relationship with body weight. Furthermore, all but 2 of the outliers were within the range for mean IVA AUC when given as monotherapy in this age range (10.8 to 15.3 hr.µg/mL). Median LUM AUC in the 6 – 11 years age group was of the order of 10% lower than in the older age groups. Median IVA AUC was of the order of 30% higher in the 6 – 11 years age group compared with the older age groups.

Although there are moderate differences in the IVA AUC_{0-12h}, the observed trough concentrations for subjects 6 through 11 years of age are similar of those of older subjects, particularly for Study 109. To maintain trough concentrations that are comparable to the older population, the AUC_{0-12h} needs to be higher for subjects 6 through 11 years of age. This is due to the differences in allometric scaling (i.e. different exponents) for clearance and volume of distribution with weight. For a similar range of C_{trough} values in the older population, the peak concentration and the corresponding AUC will be higher in subjects 6 through 11 years of age. The principle that higher IVA exposure is needed to maintain trough IVA concentrations comparable to those in the older age group is accepted. Nonetheless, the acceptability of the AUC outliers is in part derived from comparison with the mean IVA AUC when given as monotherapy at a dose of 150 mg twice daily. Since the initial approval of IVA as monotherapy, model-based simulations have resulted in a downwards revision of dose in children weighing less than 25 kg to 75 mg twice daily. In the responses to the CHMP's request it was confirmed that even at the revised dose of Kalydeco of 75 mg q12h in 6 – 11 year olds weighing 14–25 kg, mean IVA AUC is still substantively higher than with Orkambi in the age appropriate formulation administered to the 6-11 year old, 14–25 kg group .

Comparisons of IVA exposure between Orkambi and Kalydeco in the 6-11 year old age group are therefore valid for the revised lower dose of Kalydeco in children weighing less than 25 kg.

The use of an age cut-off of 11 years, beyond which the higher strength formulation should be used, without dose adjustment for body weight, is supported by the Pop PK analysis. The MAH's conclusions from the PopPK analysis are therefore overall endorsed by the CHMP.

There is minimal renal excretion of parent LUM/IVA drug and metabolites. The Pop PK analysis supplied with the original dossier indicated no effect of mild or moderate renal impairment on PK. Therefore no dose adjustment is necessary for patients with mild to moderate renal impairment. However, given that uraemia can affect hepatic clearance, section 4.2 in the SmPC includes the warning that caution is recommended while using Orkambi in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or end-stage renal disease. The current recommendations for impaired renal function are adequate for the new formulation in the 6 – 11 year old age group.

In the original dossier, 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. The SmPC therefore recommends dose reduction 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 is recommended to be used with caution at a maximum dose of lumacaftor 400 mg/ivacaftor 250 mg total daily dose in patients 12 years and older, or lumacaftor 200 mg/ivacaftor 250 mg total daily dose in children 6 to 11 years of age, given as one tablet in the morning and one tablet in the evening.

The same recommendations are therefore made for the two age groups: a 25% reduction in total daily dose in moderate hepatic impairment and to be used with caution in severe hepatic impairment, to a maximum total daily dose 50% of that normally recommended, given as one tablet twice a day. The table with recommendations for dose modifications in hepatic impairment in section 4.2 of the SmPC has been suitably amended. In addition to the potential effect on drug clearance of hepatic impairment, the possibility of drug-related hepatic toxicity has also been considered. This is discussed further in section 2.6.

In the 6 – 11 year old patients studied in 011B and 109, slightly more female compared with male patients were studied (95 girls versus 70 boys). Literature data indicate that females with CF tend to fare worse than males in terms of clinical course of disease and females die on average 2- 3 years earlier than males with CF. LUM/IVA exposure was similar in boys and girls. The vast majority of 6 – 11 year old patients studied thus far were white Caucasian with only one patient from a different racial background represented in study 109. Cystic fibrosis is more common in Caucasian patients than in those of African or Asian racial origin and the prevalence of the F508del CFTR homozygous genotype is even lower in non-Causcasian compared to Caucasian patients. The available PK data suggest similar exposure LUM and IVA exposure profiles in non-Caucasian patients; the data are limited but reflective of the low incidence of patients homozygous for F508del CFTR in the non-Caucasian population.

The median survival for patients with CF born in 2014 is 40.0 years. The oldest individual studied was 57 years of age. Data in older patients 65 years and over are therefore not available.

2.4.3. Pharmacodynamics

Mechanism of action

Lumacaftor is presumed to partially overcome the folding defect in F508del-CFTR, facilitating its correct cellular processing and trafficking, 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 delivered to the cell surface by lumacaftor can be potentiated by ivacaftor to further enhance chloride transport. When added in vitro to F508del/F508del human bronchial epithelial cells (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

Primary pharmacology: Study 011B evaluated change from baseline sweat chloride, accepted as a pharmacodynamic readout of CFTR function, in response to LUM/IVA treatment. There was an improvement (reduction) in sweat chloride by Day 15 that was sustained through Week 24. The LS mean absolute change from baseline in sweat chloride at Week 24 was -24.8 mmol/L (95% CI: -29.1, -20.5; P<0.0001). The magnitude of the change from baseline in sweat chloride, with reversal on treatment discontinuation supports a relevant pharmacodynamic effect, consistent with at least partial correction of the core biochemical defect and the proposed mechanism of action for the fixed drug combination, in the 6 – 11 years age group at the proposed posology.

In Study 011B BMI, weight and height increased from baseline consistent with improved pancreatic function and improved nutritional status. Treatment with LUM/IVA resulted in favourable changes in the CFQ-R respiratory domain score (Version: “Children Ages 6 to 11”). The LS mean absolute change from baseline in the CFQ-R respiratory domain score at Week 24 was 5.4 points (95% CI: 1.4, 9.4; P = 0.0085). CFQ-R is the best validated of the patient reported outcomes in cystic fibrosis. CFQ-R is a symptom rather than Quality of Life Score which is more difficult to assess in the paediatric population. According to the report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012) the minimum clinically important difference (MCID) is 4 in patients with stable disease.

The spirometry endpoint $ppFEV_1$ was evaluated as a safety as well as PD endpoint due to concerns over the observation of a transient bronchoconstrictive effect of Orkambi in adolescents and adults, in case this may be more pronounced in younger children with smaller diameter airways. There was an overall improvement from baseline in ppFEV1 by 24 weeks, suggesting the potential for some degree of reversal of lung function deficit in patients at an earlier stage of disease. However, there was also a transient decline in mean $ppFEV_1$ between 4 and 8 weeks although this was not substantial (between 1 and 2 percentage points); nonetheless, the decline was potentially clinically significant in some patients. By 16 weeks the mean $ppFEV_1$ had recovered to higher than baseline values and continued to demonstrate some improvement beyond this. There was an overall low rate of treatment discontinuation in study 011B (2

patients discontinued due to AEs) and therefore the PD outcome at 24 weeks can be considered to reflect the study population as a whole.

Study 011B allowed the inclusion of subjects with ppFEV1 at screening ≥ 40 (compared to study 109 where ppFEV1 ≥ 70 was an inclusion criterion). Although subjects with lower ppFEV1 values at baseline might be considered more susceptible to an initial bronchoconstrictive effect, it is also possible that patients with lower baseline values could be less sensitive to revelation of decline over a short time period. In the applicant's response during the evaluation, it was clarified that only 3 subjects had a baseline ppFEV1 <70 and there was no evidence of a trend suggesting they were more likely to experience bronchoconstriction on treatment initiation, which was reassuring.

The multiple breath washout (MBW) test lung clearance index $LCI_{2.5}$ was evaluated as an exploratory endpoint. The guideline on clinical development of medicinal products for the treatment of cystic fibrosis EMEA/CHMP/EWP/9147/2008-corr* recommends FEV_1 as an efficacy endpoint. However, the report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012) acknowledges that in younger patients with milder disease, and in whom respiratory function as determined by spirometry may not have begun to decline, FEV_1 may not be sufficiently sensitive to detect a treatment effect. Indeed, this is suggested by the $ppFEV_1$ results in study 011B which were nonetheless overall encouraging in suggesting potential for improvement in respiratory function. The same report also recommends that in younger patients, a more sensitive endpoint such as LCI should be evaluated, although the limited clinical experience of this as an outcome measure, and the lack of an established clinically relevant magnitude of benefit, are also acknowledged. There was a clear decline (reflecting improvement) in $LCI_{2.5}$ from baseline through to 24 weeks (LS mean change from baseline -0.94 (95% CI: -1.38, -0.51; P = 0.0002) through Week 24 which is consistent with the trend to improvement in ppFEV1 over the same period. The improvement in LCI was sustained at least in the early phase of the washout period. Overall, the exploratory PD and efficacy data from study 011B provide support that the new FDC of Orkambi at the proposed posology acts in a manner consistent with the primary pharmacology in this patient population.

Secondary pharmacology: Secondary pharmacology studies were confined to study of the effects of the combination LUM/IVA on QTc. These were evaluated in the initial marketing authorisation application. In the context of the line extension, mean IVA Cmax concentrations in 6 – 11 year olds in study 109, despite being approximately two fold higher than children 12 years and above administered with the age appropriate posology, are more than 5 fold lower than IVA Cmax concentrations in the dedicated IVA tQT study (0.821 versus 5.45 µg per ml). Mean LUM Cmax concentrations in 6 to 11 year old CF patients receiving an age appropriate dose of LUM/IVA are approximately two fold lower than those in the LUM/IVA tQT healthy volunteer study. The tQT study findings are therefore applicable to 6-11 year old CF patients receiving the age-appropriate formulation of Orkambi.

Pharmacokinetic /pharmacodynamic relationship

Pharmacokinetic /pharmacodynamic (PK/PD) modelling data (patients 12 years and above) showed 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 appeared moderate and the effect of the covariates did not seem to be significant. No additional PK-PD modelling data has been provided in the line extension. Although LUM and IVA exposures are comparable in the two age ranges administered with the appropriate combination, the applicant was requested by the CHMP to provide PK-

PD modelling data for the relationship between the primary efficacy endpoint, LCI 2.5, selected for the pivotal study, and exposure to LUM and IVA if this is available or to justify its absence.

Results in CF patients 12 years and older showed a linear relationship between FEV1 and lumacaftor plasma concentration. No exposure-response (E-R) trends have been identified between LUM and IVA exposure and change from baseline in lung clearance index (LCI) in the 6-11 year old patients. Exposure-efficacy data for $LCI_{2.5}$ in 6 – 11 year olds are limited as a single dose was evaluated. Furthermore, plasma exposure may be poorly reflective of active substance concentrations at the target sites, given that the site of action of Orkambi (lumacaftor) is likely to be at least in part intracellular and therefore pharmacological activity will ultimately be governed by levels inside the cell, this in turn being influenced by regulation of cellular uptake and retention as well as plasma concentrations. Furthermore, an efficacy endpoint with greater sensitivity such as LCI 2.5 is more likely to reveal variability in efficacy-exposure particularly in a relatively small sample. The lack of a demonstrable exposure-efficacy response for $LCI_{2.5}$ is considered overridden by the overall efficacy conclusions, which is acceptable for the CHMP.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology of Orkambi in the new FDC in the age range proposed in the line extension is overall supported by the data provided. Although the use of two different exponents for allometric scaling across paediatric subpopulations is not recommended, if the popPK model is developed to include children below 6 years of age, the MAH is encouraged to use the same allometric exponent for all paediatric age groups. The CHMP was of the opinion that that the CYP3A induction mediated via lumacaftor and affecting the ivacaftor CL should be adequately described in the model to ensure that the allometric exponent, if estimated, is not confounded by any effect of induction but solely reflects the effect of weight on CL.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology data provided for this extension of indication of Orkambi for use in children 6-11 years old is considered adequate by CHMP.

2.5. Clinical efficacy

A single confirmatory efficacy and safety study VX14-809-109 (abbreviated to study 109) is provided to support the extension of indication to the 6 to 11 years age group. The exploratory PD study 011B described below provides supportive efficacy data.

2.5.1. Dose response study

Study 011 (parts A and B), discussed in section 2.4, was used to inform dosing regimen for the pivotal efficacy study 109 for the line extension in 6-11 year olds. In study 011 CF subjects, 6-11 years old, were treated for 2 weeks (Part A, 10 subjects)) or for 24 weeks (Part B, 58 subjects) twice daily with 200 mg lumacaftor in combination with 250 mg ivacaftor. All subjects were homozygous for the mutation F508del-CFTR. PK modelling was used to inform a 50% dose reduction for lumacaftor while maintaining the same dose of ivacaftor in the 6 – 11 year old F508del-CFTR CF patients. The altered ratio of LUM:IVA is reflected in the new FDC of Orkambi (100 mg LUM/ 125 mg IVA) for use in the 6 – 11 year age group.

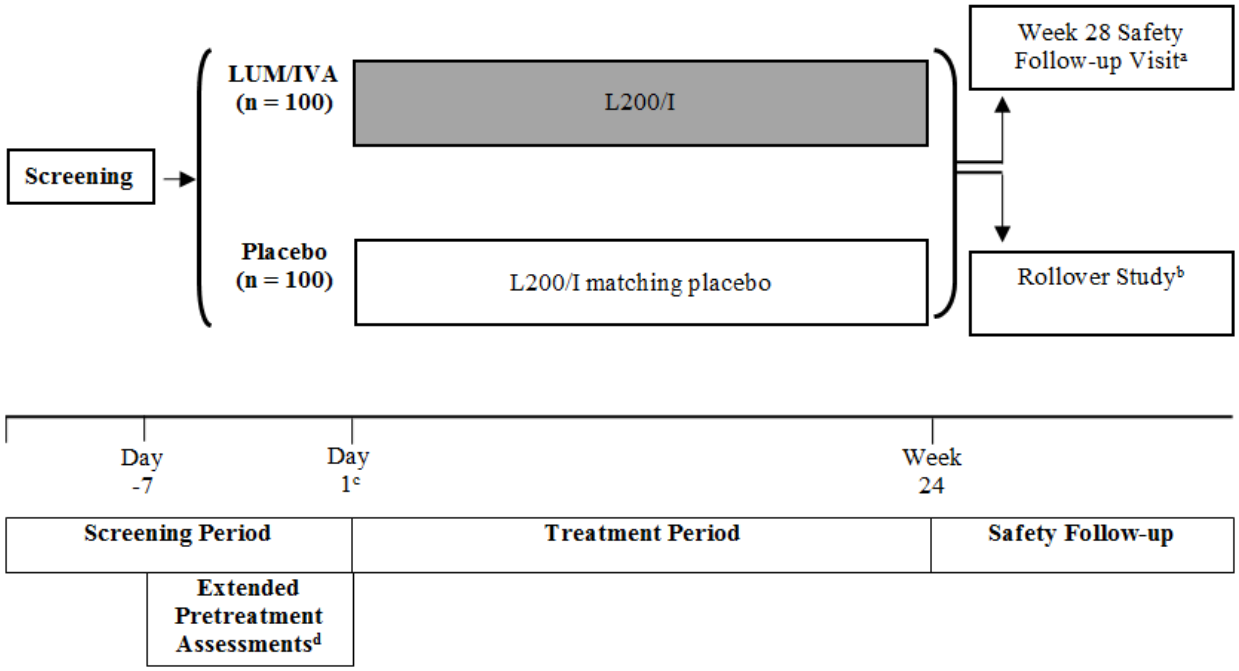
Study 011A and 011B provided PK, PD and safety and tolerability data to support adequacy of exposure to LUM and IVA with the new FDC formulation at the proposed posology in the 6 – 11 year age group, compared with F508del-CFTR CF patients 12 years and older administered with the age appropriate formulation. PK modelling was used to derive population-predicted data in the 6 – 11 year old age group. The reduction in the LUM:IVA ratio is supported by ivacaftor's AUC in most 6-11 year old subjects remaining within the 5th to 95th percentile boundaries established in the older population, using the same dose of ivacaftor although it tended to be higher. Median AUC for IVA was 30% higher in 6 – 11 year olds compared to 12 – 17 year olds and 50% higher than in adults. Ivacaftor Ctrough was similar across all age groups.

2.5.2. Main study

Study 109: A Phase III, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation

Methods

The schematic of Study 109 Design is depicted below:



FEV$_1$: forced expiratory volume in 1 second; IVA: ivacaftor; LUM: lumacaftor; L200/I: LUM 200 mg/IVA 250 mg q12h; pbo: placebo; q12h: every 12 hours

[a] The Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the last dose. The Week 28 Safety Follow-up Visit was not required for subjects who permanently discontinued study drug treatment before the Week 16 Visit or for subjects who enrolled in the Treatment Cohort of the rollover study within 28 days after the last dose of study drug.

[b] At the Week 24 Visit of Study 109, subjects who completed study drug treatment and the visits in the Treatment Period were offered the opportunity to enroll in the Treatment Cohort of an optional open-label rollover study (Study 110) evaluating LUM/IVA for an additional 96 weeks. Subjects who permanently discontinued study drug treatment but who completed the visits in the Treatment Period were offered the opportunity to enroll in the Observational Cohort of the rollover study.

[c] Approximately 200 subjects were to be stratified by weight (<25 kg versus ≥25 kg) and percent predicted FEV1 severity (<90 versus ≥90), both as determined at the Screening Visit, and randomized (1:1) before the first dose of study drug on Day 1

[d] The Extended Pretreatment Assessment Period was included for subjects at a subset of sites participating in the Imaging Substudy.

Study Participants

Subjects were 6 – 11 years old, males and females, with a confirmed diagnosis of CF defined as 2 CF-causing mutations in addition to either chronic sinopulmonary disease and/or gastrointestinal/nutritional abnormalities. Subjects were homozygous for *F508del-CFTR.* Genotyping was performed using a validated CF genotyping test. Enrolment was limited to subjects with $LCI_{2.5}$ result ≥ 7.5 at the Screening Visit (normal value <7.5). Spirometry at baseline ($ppFEV_1$) could be normal (pp FEV_1 >70). Subjects with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g., cirrhosis with portal hypertension, risk factors for Torsades de Pointes) were excluded from Study 109. Subjects with protocol-defined laboratory values indicative of clinically significant abnormal liver or renal function were also excluded (any of ≥ 3 x ULN two or more of AST, ALT, GGT, ALP; ≥ 5 x ULN ALT or AST; total bilirubin >2 × ULN; GFR ≤ 45 mL/min/1.73 m^2 calculated by the Counahan-Barratt equation). These criteria were comparable to studies 103 and 104.

Treatments

The active treatment was LUM 200 mg/IVA 250 mg q12h. It was recommended that subjects remain on a stable CF medication regimen from 4 weeks before Day 1 through Week 24 or, if applicable, through the Safety Follow-up Visit. Information about bronchodilator use was collected and documented. Subjects who used a bronchodilator had their spirometry assessments performed according to the guidelines specified in the protocol. Other concomitant medications were prohibited if the potential existed for untoward drug-drug interactions, such as strong CYP3A4 inducers and strong CYP3A4 inhibitors.

Objectives

The primary objective was to evaluate efficacy of LUM/IVA in subjects aged 6 through 11 years with CF, homozygous for the *F508del-CFTR* mutation.

Secondary objectives were:

- To evaluate the safety of LUM/IVA
- To investigate the pharmacokinetics (PK) of LUM and its metabolite (M28-LUM) and IVA and its metabolites (M1-IVA and M6-IVA)

Outcomes / endpoints

Study Identifier	Study Design and Type of Control	Study Centers	Key Inclusion Criteria	Treatment	Number of Subjects Dosed/ Completed Treatment/ Completed Study	Duration of Treatment	Primary and Secondary Efficacy Endpoints[a]
Study 109	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	54 sites in North America, Europe, and Australia	• Confirmed diagnosis of CF • Homozygous for *F508del* • 6 through 11 years of age	LUM 200 mg/ IVA 250 mg q12h	204[b]/193/196	24 weeks	Primary Absolute change in $LCI_{2.5}$ from baseline through Week 24 Key Secondary • Average absolute change in sweat chloride from baseline at Day 15 and at Week 4 • Absolute change in BMI from baseline at Week 24 • Absolute change in CFQ-R respiratory domain score from baseline through Week 24 Other Secondary • Absolute change in $LCI_{5.0}$ from baseline through Week 24 • Absolute change in sweat chloride from baseline at Week 24 • Absolute change in $ppFEV_1$ from baseline through Week 24 • Relative change in $ppFEV_1$ from baseline through Week 24 • Absolute change in BMI-for-age z-score from baseline at Week 24 • Absolute change in weight from baseline at Week 24 • Absolute change in weight-for-age z-score from baseline at Week 24 • Absolute change in height from baseline at Week 24 • Absolute change in height-for-age z-score from baseline at Week 24 • Absolute change in TSQM domains from baseline through Week 24 • Time-to-first PEx through Week 24 • Event of having at least 1 PEx through Week 24 • Number of PExs through Week 24

BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FE-1: fecal elastase-1; IVA: ivacaftor; IRT: immunoreactive trypsinogen; LCI: lung clearance index; LUM: lumacaftor; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; TSQM: Treatment Satisfaction Questionnaire for Medication

[a] Other efficacy endpoints were absolute change in FE-1 levels from baseline at Week 24, absolute change in serum levels of IRT from baseline through Week 24, and absolute change in sputum microbiology from baseline at Week 24.

[b] There were 19 subjects who participated in the exploratory Imaging Substudy.

Primary efficacy endpoint: Study 109 evaluated absolute change in $CI_{2.5}$ from baseline as the primary endpoint. The primary efficacy analysis compared the change from baseline $LCI_{2.5}$ in active and placebo arms.

Secondary efficacy endpoints are listed in the table above and included analyses of lung function (LCI and spirometry), sweat chloride, nutritional indices (body mass index [BMI], weight, height, and associated z-scores for each), Cystic Fibrosis Questionnaire-Revised [CFQ-R] responses, Treatment Satisfaction Questionnaire for Medication [TSQM] responses, and clinical events related to outcomes (e.g., PExs). Other evaluations included analyses of faecal elastase-1 (FE-1), immunoreactive trypsinogen (IRT), and sputum microbiology. An exploratory evaluation of imaging results was also included.

$ppFEV_1$ was a secondary endpoint (expressed as percent predicted value based on age, height, and sex) because it was expected that the majority of subjects would have well-preserved spirometry at baseline. $ppFEV_1$ values were calculated from regression equations derived from a healthy reference population to allow the comparison of values over time for a growing individual and across subjects. The Wang reference equations were selected because the reference values across the studied ages are estimated more precisely and accurately. Spirometry was performed according to the internationally-recognized American Thoracic Society/European Respiratory Society Guidelines.41 Furthermore and were performed before inhalation of a bronchodilator to minimize confounding effects on FEV1.

The sweat chloride test was included as an in vivo PD measure of the effect of LUM/IVA on CFTR activity. Collection of sweat samples was performed using an approved collection device. At each time point, 2 samples were collected, 1 sample from each arm (left and right).

BMI was measured to assess nutritional status and is recognised as an appropriate endpoint for therapies targeting pancreatic insufficiency as well as systemic therapies targeting the biochemical defect in the CFTR.

The CFQ-R is a validated CF-specific instrument that measures the health-related quality of life of patients with CF. The CFQ-R measures quality-of-life domains including respiratory symptoms, digestive symptoms, emotion, and health perception. CFQ-R has been evaluated in clinical studies involving therapies for CF lung disease. CFQ-R assessments were performed in a standardized manner. The CFQ-R was completed before the start of any assessments, including other questionnaires. Two versions of the CFQ-R were used: 1 in which the information was self-reported in an interviewer format ("Children Ages 6 to 11") and 1 in which the subject's parent or caregiver was the respondent ("Parents/Caregivers"). The "Children Ages 6 to 11" version is the primary version in this age group. The minimal clinically important difference (MCID) score of 4.0 corresponds to the adolescent/adult version of the CFQ-R respiratory domain (subjects 14 years of age and older).

TSQM (Treatment Satisfaction Questionnaire for Medication) is a widely used generic measure of satisfaction with medication. It was originally validated in a sample of patients with a variety of chronic conditions, but has been demonstrated to be a valid and reliable measure of satisfaction in patients with CF. TSQM domains measure effectiveness, side effects, convenience, and global satisfaction. Because treatment satisfaction is not measured with the other health-related quality-of-life measures evaluated in Study 109, the TSQM was included as a study assessment.

CF pulmonary exacerbations (PExs) are a combination of signs and symptoms that often herald a need for aggressive treatment including IV antibiotics and may require hospitalisation. PExs are the major cause of morbidity and decreased quality of life for patients with CF. The number of events, estimates of event rates, time-to-onset, and the duration of PExs including those involving hospitalizations and IV antibiotic therapy are clinically important endpoints to both clinicians managing patients with CF and the patients themselves. However, PEx events are less common in children than adults, and therefore it is more difficult to identify an effect of treatment on this endpoint in younger subjects.

There is no generally accepted definition of a PEx and large multicentre CF clinical studies have used various physician-derived definitions. For data consistency, a single definition of PEx was specified for Study 109, based on that used for other studies including Studies 103 and 104 and initial IVA registration studies. PEx was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection.

Sample size

The sample size was pre-specified as 200 subjects and with this, 100 subjects/arm and 10% missing data/dropout rate, the study had approximately 90% power to detect a treatment difference of 0.68 at a 2-sided 0.05 significance level, assuming a standard deviation of 1.4 based on VX10-770-106 data. The sample size of 35 subjects planned for the Imaging Substudy was driven by feasibility considerations. No formal sample size calculation was performed.

Randomisation

200 subjects, who met the eligibility criteria, were to be randomised (1:1) to 1 of the 2 treatment arms, stratified by weight (<25 kg versus ≥ 25 kg) and ppFEV$_1$ severity (<90 versus ≥ 90), as determined at the Screening Visit. Randomisation occurred after all inclusion and exclusion criteria were met and before the first dose of study drug. Randomisation may have occurred on Day -1.

Blinding (masking)

Subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded, with the exception of study personnel identified in the protocol. Subjects and their parent/caregiver were not informed of their study-related LCI, spirometry, sweat chloride, and imaging results during the study regardless of whether the subject had prematurely discontinued treatment.

Unblinding of an individual subject's treatment by the investigator was limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment was necessary for clinical management. Procedures for unblinding were provided in the protocol. Vertex Global Patient Safety (GPS) or designee was permitted to unblind any serious AE (SAE) reports in compliance with regulatory reporting requirements. In addition, Vertex were able, for matters relating to safety concerns, to unblind individual subjects at any time.

Statistical methods

The statistical analysis plan (SAP) was developed and finalised before database lock. The following analysis sets were defined:

- All Subjects Set was defined as all subjects who were randomised or dosed (i.e., all subjects in the study). All subject data listings were referenced using the All Subjects Set, unless otherwise specified.
- Full Analysis Set (FAS) included all randomised subjects who were exposed to any amount of study drug. The treatment assignment for the FAS was as randomised.
- The FAS was used for all efficacy analyses, except the endpoints related to imaging assessments.
- Safety Set included all subjects who were exposed to any amount of study drug. The treatment assignment for the Safety Set was as treated. For subjects who received study drug from placebo and active treatment groups during the trial, the treatment group allocation for as-treated analysis was the active treatment group.
- The Safety Set was used for all safety analysis.
- Imaging Substudy Set was defined as a subset of FAS who or whose caregiver consented to the Imaging Substudy per supplemental informed consent and assent. The Imaging Substudy Set was used for the analysis related to imaging assessments.

Efficacy analyses were performed using the FAS. Analyses were performed for the following primary and secondary efficacy endpoints: (1) absolute change in LCI$_{2.5}$ from baseline through Week 24; (2) average absolute change in sweat chloride from baseline at Day 15 and at Week 4; (3) absolute change in BMI from baseline at Week 24; (4) absolute change in CFQ-R respiratory domain score from baseline through

Week 24; (5) absolute change in $LCI_{5.0}$ from baseline through Week 24; (6) absolute change in sweat chloride from baseline at Week 24; (7) absolute change in ppFEV1 from baseline through Week 24; (8) relative change in $ppFEV_1$ from baseline through Week 24; (9) absolute change in BMI-for-age z-score from baseline at Week 24; (10) absolute change in weight from baseline at Week 24; (11) absolute change in weight-for-age z-score from baseline at Week 24; (12) absolute change in height from baseline at Week 24; (13) absolute change in height-for-age z-score from baseline at Week 24; (14) absolute change in TSQM domains from baseline through Week 24; (15) time-to-first PEx through Week 24; (16) event of having at least 1 PEx through Week 24; and (17) number of PExs through Week 24.

The primary efficacy endpoint, absolute change from baseline in LCI2.5, was analysed using a mixed model for repeated measures (MMRM). The model included the absolute change in LCI2.5 from baseline (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for weight (<25 kg versus ≥ 25 kg) and ppFEV1 severity (<90 versus ≥ 90), both as determined at the Screening Visit, and the baseline LCI2.5 as a continuous variable. The primary result obtained from the model was the absolute change from baseline in LCI2.5 through Week 24.

Analyses for secondary endpoints 2, 4 through 6, and 12 through 14 were based on an MMRM analysis similar to that used for the primary analysis, replacing baseline LCI2.5 with the baseline of the corresponding variable as a continuous covariate. Analyses for secondary endpoints 3 and 7 through 11 were based on an MMRM analysis similar to that used for the primary analysis, removing baseline LCI2.5 as a continuous covariate.

Time-to-first PEx through Week 24 was analyzed using Kaplan-Meier methods. The incidence of subjects with at least 1 PEx through Week 24 was summarized and the Mantel-Hanszel estimate of the odds ratio and the corresponding 95% CI provided. For number of PExs through Week 24, the treatment comparison was carried out using regression analysis for a negative binomial distribution.

Incomplete/Missing Data was not imputed, unless otherwise specified; i.e., all missing values remained as missing in all statistical analyses and listings, unless otherwise specified. Missing post-baseline values were not imputed for efficacy analysis conducted using a mixed model for repeated measures (MMRM) approach, which made use of all available data even if a subject had missing data at some post-baseline visits.

Results

Participant flow

In study 109, a total of 204 subjects were exposed to study drug, with 193 (94.6%) subjects completing treatment and 196 (96.1%) subjects completing the study. A total of 19 subjects participated in the Imaging Substudy. The treatment discontinuation rate was similar in the LUM/IVA (5.8%) and placebo (5.0%) groups. Overall, the most common reason for treatment discontinuation was an adverse event (AE) (2.5%). The treatment discontinuation rate due to AE was similar in the LUM/IVA (2.9%) and placebo (2.0%) groups.

Subject Disposition (Study 109, All Subjects Set)

	n (%)[a]		
Disposition/Reason	**Placebo N = 101**	**L200/I N = 103**	**Overall N = 204**
All Subjects Set[b]	102	104	206
Randomized	102	104	206
FAS[c]	101	103	204
Safety Set[d]	101	103	204
Imaging Substudy Set[e]	7	12	19
Randomized but never dosed	1	1	2
Completed treatment	96 (95.0)	97 (94.2)	193 (94.6)
Discontinued treatment	5 (5.0)	6 (5.8)	11 (5.4)
Reasons			
AE	2 (2.0)	3 (2.9)	5 (2.5)
Subject refused further dosing (not due to AE)	2 (2.0)	1 (1.0)	3 (1.5)
Lost to follow-up	0 (0.0)	1 (1.0)	1 (0.5)
Did not meet eligibility criteria	1 (1.0)	1 (1.0)	2 (1.0)
Completed study	98 (97.0)	98 (95.1)	196 (96.1)
Discontinued study	3 (3.0)	5 (4.9)	8 (3.9)
Reasons			
AE	0 (0.0)	2 (1.9)	2 (1.0)
Withdrawal of consent (not due to AE)	2 (2.0)	1 (1.0)	3 (1.5)
Lost to follow-up	0 (0.0)	1 (1.0)	1 (0.5)
Other	1 (1.0)	1 (1.0)	2 (1.0)

	n (%)[a]		
Disposition/Reason	**Placebo N = 101**	**L200/I N = 103**	**Overall N = 204**
Rollover to Study 110			
Yes	98 (96.1)	96 (92.3)	194 (94.2)
Treatment Cohort	96 (94.1)	94 (90.4)	190 (92.2)
Observational Cohort	2 (2.0)	2 (1.9)	4 (1.9)
No	4 (3.9)	8 (7.7)	12 (5.8)

Source: Module 5.3.5.1/VX14-809-109/Table 14.1.1.1
AE: adverse event; FAS: Full Analysis Set; IVA: ivacaftor; LUM: lumacaftor; L200/I: LUM 200 mg/ IVA 250 mg q12h; n: size of subsample; N: total sample size of the FAS; q12h: every 12 hours

[a] The percentages are calculated relative to the number of subjects in the FAS.
[b] All Subjects Set: All subjects who were randomized or dosed.
[c] FAS: All randomized subjects who were exposed to any amount of study drug.
[d] Safety Set: All subjects who were exposed to any amount of study drug.
e Imaging Substudy Set: A subset of the FAS subjects who or whose caregiver consented to the Imaging Substudy.

Recruitment

Study VX14-809-109 was initiated in July 2015 and completed in September 2016.

Conduct of the study

The majority of subjects (97.5%) used medication before receiving the first dose of study drug. The most common prior medications (≥ 30% incidence overall) were for CF management and included dornase alfa (86.3%), pancreatin (73.5%; pancrelipase was also used in 22.5% of subjects), sodium chloride (70.1%), and salbutamol (65.7%). The majority of subjects (99.5%) also used concomitant medication. The most common concomitant medications (≥ 30% incidence overall) were for CF management and included dornase alfa (86.8%), pancreatin (73.0%; pancrelipase was also used in 23.5% of subjects), sodium chloride (71.1%), salbutamol (67.6%), and azithromycin (34.8%). Subjects in the LUM/IVA group used vitamins not otherwise specified approximately 14% more frequently than the placebo group. Subjects in the placebo group used tobramycin and paracetamol approximately 10% to 13% more frequently than the LUM/IVA group. The use of all other concomitant medications was generally similar across the LUM/IVA and placebo groups.

Protocol deviations: 15 (7.4%) subjects had an important protocol deviation IPD (8.7% of subjects in the LUM/IVA group and 5.9% of subjects in the placebo group). The IPDs included those related to meeting exclusion criteria 3 and 8 (1.9% of subjects in the LUM/IVA group and 2.0% of subjects in the placebo group), stratification errors (2.9% of subjects in the LUM/IVA group and 1.0% of subjects in the placebo group), and compliance/number of tablets taken <80% (5.8% of subjects in the LUM/IVA group and 3.0% of subjects in the placebo group). The protocol deviations are not likely to have affected the study outcome as deemed by the applicant and the CHMP.

Baseline data

Baseline disease severity characteristics Study 109, FAS

Characteristic	Placebo N = 101	L200/I N = 103	Overall N = 204
$LCI_{2.5}$			
<7.5	5 (5.0)	3 (2.9)	8 (3.9)
≥7.5	96 (95.0)	100 (97.1)	196 (96.1)

$LCI_{2.5}$			
n	101	103	204
Mean (SD)	10.26 (2.24)	10.30 (2.36)	10.28 (2.29)
SE	0.22	0.23	0.16
Median	9.72	9.69	9.72
Min, Max	6.55, 15.82	7.10, 16.38	6.55, 16.38
Sweat chloride (mmol/L)			
n	98	102	200
Mean (SD)	103.4 (9.8)	102.6 (10.3)	103.0 (10.1)
SE	1.0	1.0	0.7
Median	104.6	104.4	104.5
Min, Max	64.5, 123.0	46.0, 119.0	46.0, 123.0
$ppFEV_1$, n (%)			
<70	1 (1.0)	10 (9.7)	11 (5.4)
≥70 to <90	47 (46.5)	42 (40.8)	89 (43.6)
≥90 to ≤105	44 (43.6)	38 (36.9)	82 (40.2)
>105	9 (8.9)	12 (11.7)	21 (10.3)
$ppFEV_1$ (percentage points)			
n	101	102	203
Mean (SD)	90.7 (10.8)	88.8 (13.7)	89.8 (12.4)
SE	1.1	1.4	0.9
Median	90.7	89.4	90.5
Min, Max	70.0, 114.7	48.6, 119.6	48.6, 119.6

Mean age- and sex-adjusted nutritional indices were -0.21 (weight-for-age z-score), -0.14 (BMI-for-age z-score), and -0.14 (height-for-age z-score). Mean LCI2.5 was 10.28 (normal value: <7.5), mean sweat chloride was 103.0 mmol/L, and mean ppFEV1 was 89.8 percentage points. A total of 87 (42.6%) subjects were positive for Pseudomonas aeruginosa at baseline. The baseline profile was generally similar across the LUM/IVA and placebo groups. Mean ppFEV1 was 88.8 in the LUM/IVA group versus 90.7 in the placebo group. The percentage of subjects who received inhaled antibiotics, inhaled corticosteroids, and inhaled hypertonic saline before the first dose was, respectively, 19.4%, 36.9%, and 65.0% in the LUM/IVA group versus 29.7%, 46.5%, and 53.5% in the placebo group.

Numbers analysed

The PK set contained data for 104 subjects. Day 1 samples for one subject were excluded from analysis as the pre-dose results were positive and the 3 to 6 hour results were below the lower limit of quantification. All efficacy analyses (except endpoints related to imaging assessments) were conducted using the FAS, which included 204 randomised subjects who were exposed to any amount of study drug. The CHMP noted that in accordance with the intention to treat principle the primary efficacy analysis should be conducted on all randomised subjects whether or not they received study medication. However, the all subjects set (ITT population) is very similar in number to the FAS (206 versus 204, with a difference of one patient in each arm). Given the similarity in ITT and FAS populations, execution of the primary efficacy analysis on the FAS is acceptable.

Outcomes and estimation

Primary efficacy endpoint – absolute change in $LCI_{2.5}$ from baseline through week 24

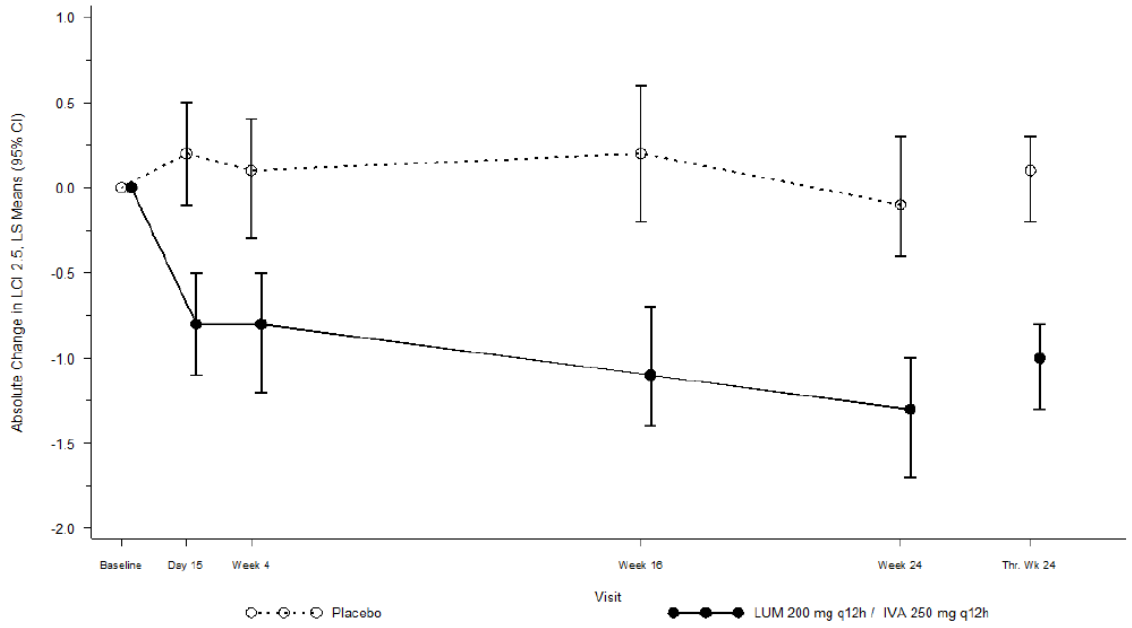
Treatment with LUM/IVA resulted in a statistically significant improvement (i.e. a reduction) in $LCI_{2.5}$ compared to placebo, with a LS mean treatment difference of -1.09 (95% CI, -1.43, -0.75) p<0.0001 for the absolute change through Week 24.

A statistically significant improvement in $LCI_{2.5}$ was observed at Day 15 and sustained through Week 24. There was no treatment-by-visit interaction (P = 0.5174).

MMRM Analysis of Absolute Change in LCI2.5 From Baseline Through Week 24 (FAS)

Statistic	Placebo N = 101	L200/I N = 103
Baseline[a]		
n	101	103
Mean (SD)	10.26 (2.24)	10.30 (2.36)
Absolute change through Week 24		
n	99	99
Mean (SD)	0.08 (1.41)	-1.00 (1.41)
LS mean (SE)	0.08 (0.13)	-1.01 (0.13)
95% CI	(-0.18, 0.34)	(-1.27, -0.75)
P value within treatment	0.5390	<0.0001
LS mean difference (SE)	-	-1.09 (0.17)
95% CI	-	(-1.43, -0.75)
P value versus placebo	-	<0.0001
P value for treatment-by-visit interaction	0.5174	-

Absolute Change in LCI2.5 From Baseline at Each Visit and Through Week 24 (FAS)



Source: Figure 14.2.1.1.1
CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LCI: lung clearance index; LS: least squares; LUM: lumacaftor; MMRM: mixed model repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours
Notes: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM analysis included treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90) at Screening. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

The percentage of missing data for the absolute change in LCI at Week 24 was 16.7%. The impact of missing data was assessed using an analysis of covariance (ANCOVA) model with missing data imputed using multiple imputations (MI) as described in CSR 109 section 9.7.4.1.3. The results of the additional analysis were consistent with the results of the primary analysis. The MI-estimated treatment difference for the LUM/IVA group compared to the placebo group was -1.20 (P = 0.0008) for the absolute change in LCI2.5 at Week 24.

Secondary efficacy endpoints

Average Absolute Change in Sweat Chloride

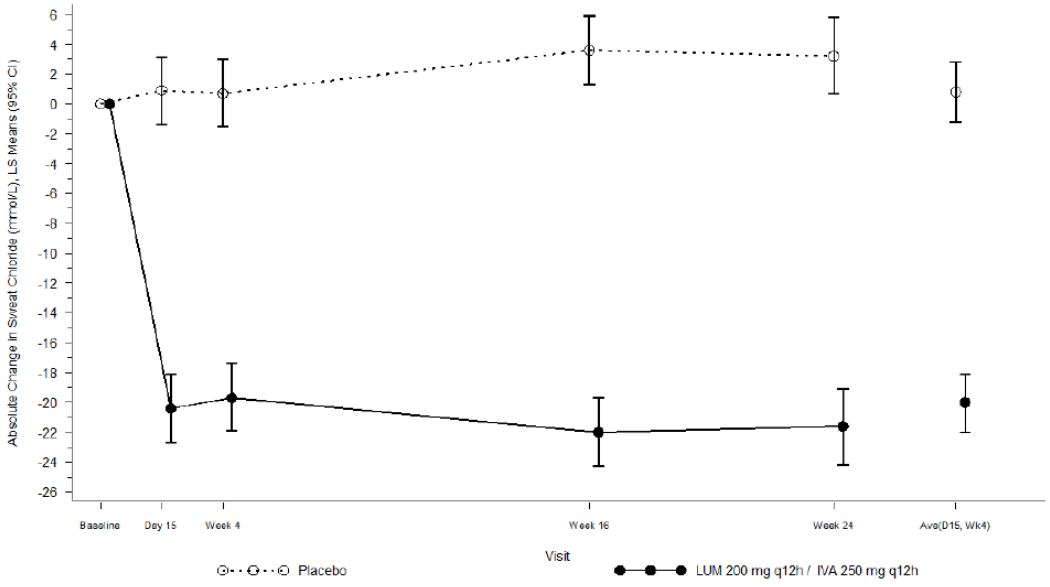
LUM/IVA resulted in improvement (i.e., a reduction) in sweat chloride was demonstrated at Day 15 and sustained through Week 24, with a LS mean treatment difference of -20.8 mmol/L (95% CI -23.4, -18.2; P<0.0001) for the average absolute change at Day 15 and at Week 4.

MMRM Analysis of Average Absolute Change in Sweat Chloride (mmol/L) From Baseline at Day 15 and at Week 4 (Study 109, FAS)

Statistic	Placebo N = 101	L200/I N = 103
Baseline		
n	98	102
Mean (SD)	103.4 (9.8)	102.6 (10.3)
Average absolute change at Day 15 and at Week 4		
n	94	95
Mean (SD)	0.5 (7.3)	-20.3 (10.9)
LS mean (SE)	0.8 (1.0)	-20.0 (1.0)
95% CI	(-1.2, 2.8)	(-22.0, -18.1)
P value within treatment	0.4208	<0.0001
LS mean difference (SE)	-	-20.8 (1.3)
95% CI	-	(-23.4, -18.2)
P value versus placebo	-	<0.0001
P value for treatment-by-visit interaction	0.0068	-

Source: Module 5.3.5.1/VX14-809-109/Table 14.2.6.2.1
CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; L200/I: LUM 200 mg/ IVA 250 mg q12h; MMRM: mixed model repeated measures; n: size of subsample; N: total sample size of the FAS; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; SD: standard deviation; SE: standard error
Notes: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. *P* values are from an MMRM analysis that included treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90) at Screening. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Absolute Change in Sweat Chloride (mmol/L) From Baseline at Each Visit and Average Absolute Change From Baseline at Day 15 and at Week 4 (Study 109, FAS)



Source: Module 5.3.5.1/VX14-809-109/Figure 14.2.6.1
CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; MMRM: mixed model repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours
Notes: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM analysis included treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90) at Screening. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Absolute Change in BMI

Treatment with LUM/IVA resulted in an improvement in BMI at Week 24, although this was not statistically significant compared to placebo. The LS mean treatment difference was 0.11 kg/m2 (95% CI -0.08, 0.31; P = 0.2522) for the absolute change in BMI at Week 24.

Absolute Change in CFQ-R Respiratory Domain

Treatment with LUM/IVA resulted in an improvement in CFQ-R respiratory domain score (Version: Children Ages 6 to 11) through Week 24, although this was not statistically significant compared to placebo. The LS mean treatment difference was 2.5 points (95% CI -0.1, 5.1; P = 0.0628) for the absolute change in CFQ-R respiratory domain score through Week 24.

Absolute change in $LCI_{5.0}$

LUM/IVA resulted in a statistically significant improvement (i.e., a reduction) in $LCI_{5.0}$ compared to placebo, with a LS mean treatment difference of -0.44 (P<0.0001) for the absolute change through Week 24.

Absolute and Relative Changes in ppFEV1

Treatment with LUM/IVA resulted in a statistically significant improvement in $ppFEV_1$ compared to placebo, with a LS mean treatment difference of 2.4 percentage points (CI 0.4, 4.4; P = 0.0182) for the absolute change through Week 24 and 3.2% (CI 0.6, 5.7; P = 0.0141) for the relative change through Week 24 (Table 5 and Figure 8 below).

MMRM Analysis of Absolute and Relative Changes in ppFEV1 From Baseline Through Week 24 (Study 109, FAS)

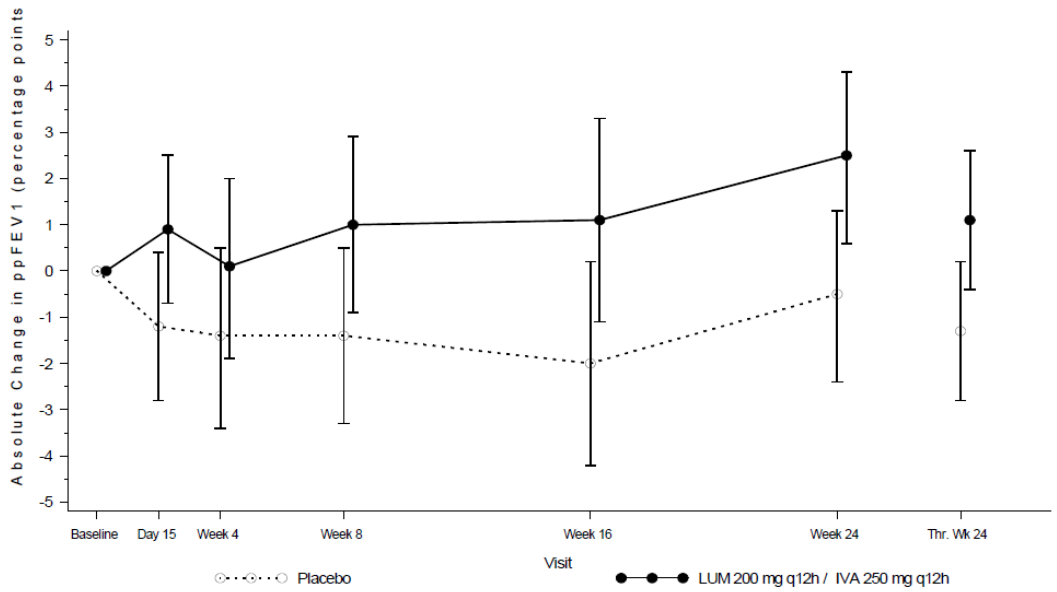
Statistic	Placebo N = 101	L200/I N = 103
Baseline		
n	101	102
Mean (SD)	90.7 (10.8)	88.8 (13.7)
Absolute change through Week 24		
n	100	101
Mean (SD)	-1.9 (6.8)	0.5 (8.1)
LS mean (SE)	-1.3 (0.8)	1.1 (0.8)
95% CI	(-2.8, 0.2)	(-0.4, 2.6)
P value within treatment	0.0899	0.1483
LS mean difference (SE)	-	2.4 (1.0)
95% CI	-	(0.4, 4.4)
P value versus placebo	-	0.0182
Relative change through Week 24		
n	100	101
Mean (SD)	-1.7 (7.8)	1.5 (11.1)
LS mean (SE)	-0.9 (1.0)	2.2 (1.0)
95% CI	(-2.8, 1.0)	(0.3, 4.1)
P value within treatment	0.3278	0.0218
LS mean difference (SE)	-	3.2 (1.3)
95% CI	-	(0.6, 5.7)
P value versus placebo	-	0.0141

Sources: Module 5.3.5.1/VX14-809-109/Table 14.2.2.2.1 and Table 14.2.2.2.2

CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; L200/I: LUM 200 mg/ IVA 250 mg q12h; MMRM: mixed model repeated measures; n: size of subsample; N: total sample size of the FAS; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; SD: standard deviation; SE: standard error

Notes: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. *P* values are from an MMRM analysis that included treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90) at Screening. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Absolute Change in ppFEV1 From Baseline at Each Visit and Through Week 24 (Study 109, FAS)

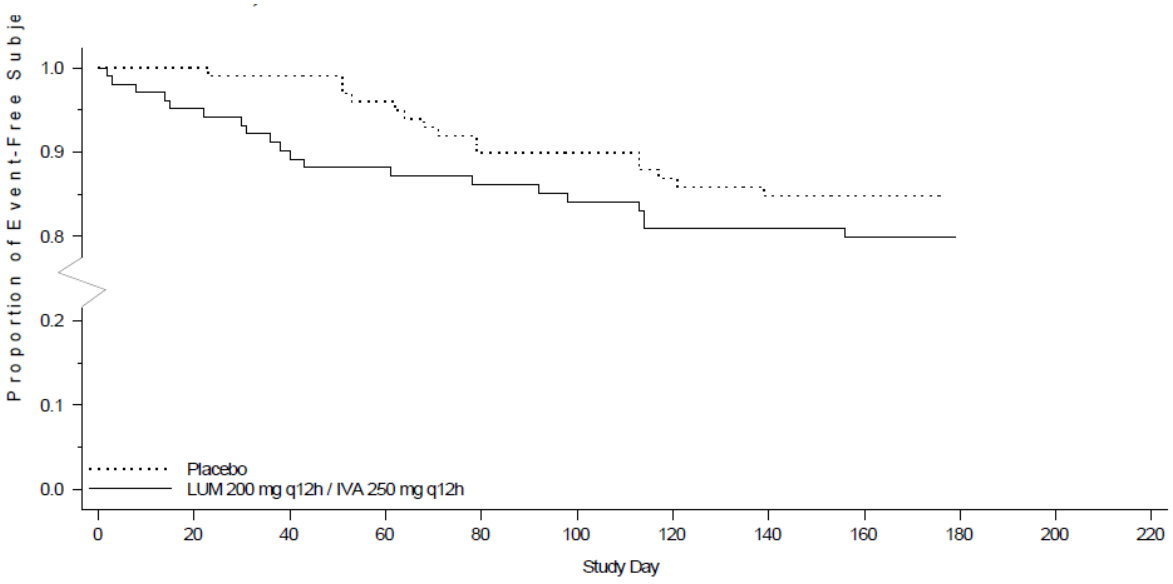


Source: Module 5.3.5.1/VX14-809-109/Figure 14.2.2.1.1
CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; MMRM: mixed model repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours
Notes: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM analysis included treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustments for weight (<25 kg versus ≥25 kg) and $ppFEV_1$ severity (<90 versus ≥90) at Screening. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Time-to-First Pulmonary Exacerbation

Kaplan-Meier analysis of time to first pulmonary exacerbation demonstrated no treatment effect with similar event-free probability between LUM/IVA and placebo: 0.800 (95% CI 0.707, 0.866) for LUM/IVA and 0.849 (0.761, 0.906) for placebo, in favour of placebo (19.4 % of LUM/IVA patients had events compared with 14.9% of placebo patients).

Time-to-First Pulmonary Exacerbation Through Week 24 (Study 109, FAS)



Source: Module 5.3.5.1/VX14-809-109/Figure 14.2.5.1
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; LUM: lumacaftor; PEx: pulmonary exacerbation; q12h: every 12 hours
Notes: Event-free probabilities are cumulative Kaplan-Meier estimates. For subjects who completed 24 weeks of treatment, subjects without a PEx before treatment completion were considered censored at the time of treatment completion or at the Week 24 Visit (whichever occurred last). For subjects who prematurely discontinued treatment, subjects without a PEx through the Week 24 Visit were considered censored at the time of the Week 24 Visit (or at the last visit before the Safety Follow-up Visit if there was no Week 24 Visit).

Ancillary analyses

Not applicable.

Summary of main study

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

Summary of efficacy for trial VX14-809-109 (abbreviated to study 109)

Title: A Phase III, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation		
Study identifier	VX14-809-109 (EudraCT number 2015-000543-16)	
Design	Randomised, double-blind, placebo-controlled, parallel group, multicentre	
	Duration of main phase:	24 weeks
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	4 week safety follow-up

Hypothesis	Superiority		
Treatments groups	active		<LUM 200 mg / IVA 250 mg q12h for 24 weeks, 104 subjects randomised to active
	Placebo		<matching LUM/IVA placebo q12h, 24 weeks, 102 randomised to placebo
Endpoints and definitions	Primary endpoint	Absolute change in $LCI_{2.5}$	Absolute change in $LCI_{2.5}$ from baseline through Week 24
	Key secondary endpoint	Absolute change in sweat chloride	Average absolute change in sweat chloride from baseline at Day 15 and at Week 4
	Key secondary endpoint	Absolute change in BMI	Absolute change in BMI from baseline at Week 24
	Key secondary endpoint	Absolute change in CFQ-R	Absolute change in CFQ-R respiratory domain score from baseline through Week 24
Results and Analysis			
Analysis description			
Analysis population and time point description	**Primary Analysis**		
Descriptive statistics and estimate variability	Full Analysis Set		

Descriptive statistics and estimate variability	Treatment group	LUM/IVA	Placebo
	Number of subject	103	101
	Absolute change in $LCI_{2.5}$ through Week 24 (LS Mean)	-1.01	0.08
	95% CI	-1.27, -0.75	-0.18, 0.34
	Absolute change in sweat chloride endpoint (LS Mean)	-20.0	0.8
	95% CI	-22.0, -18.1	-1.2, 2.8
	Absolute change in BMI	0.38	0.27

	(LS Mean)		
	95% CI	0.25, 0.52	0.13, 0.41
	Absolute change in CFQ-R (LS Mean)	5.5	3.0
	95% CI	3.4, 7.6	1.0, 5.0

Effect estimate per comparison	Primary endpoint $LCI_{2.5}$	Comparison groups	LUM/IVA vs placebo
		Treatment difference	-1.09
		95% CI	-1.43, -0.75
		P-value	<0.0001
	Secondary Endpoint Sweat chloride	Comparison groups	LUM/IVA vs placebo
		Treatment difference	-20.8
		95% CI	-23.4, -18.2
		P-value	<0.0001
	Secondary endpoint BMI	Comparison groups	LUM/IVA vs placebo
		Treatment difference	0.11
		95% CI	-0.08, 0.31
		P-value	0.2522
	Secondary endpoint CFQ-R	Comparison groups	LUM/IVA vs placebo
		Treatment difference	2.5
		95% CI	-0.1, 5.1
		P-value	0.0628

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

Not applicable.

Clinical studies in special populations

Not applicable since only patients 6-11 years old were studied.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 109 was a Phase III, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in CF patients aged 6 - 11 years, homozygous for the *F508del-CFTR* mutation.

Efficacy, safety, and PK profiles for LUM/IVA in subjects 12 years of age and older, homozygous for F508del had previously been established (Studies 103 and 104). It is not uncommon for patients in the 6- to 11-year age group to have well-preserved or even normal spirometry (e.g., percent predicted forced expiratory volume in 1 second [ppFEV1]). However, even with normal spirometry, patients in this age group with severe CF-causing mutations already have pulmonary structural aberrations observed through computed tomography (CT) scans. Consistent with this, impaired lung clearance index (LCI), which measures the degree of small airway disease by assessing ventilation inhomogeneity, can be observed in paediatric patients with normal spirometry. These observations confirm that the disease process that results from a lack of CFTR activity begins early in life and before lung function as assessed by spirometry is affected. Because the underlying genetic and molecular aetiology of the disease is consistent between this age group and older patients, it was anticipated that LUM/IVA would be efficacious in this population as well.

Subjects were 6 – 11 years old, males and females, with a confirmed diagnosis of CF defined as 2 CF-causing mutations in addition to either chronic sinopulmonary disease and/or gastrointestinal / nutritional abnormalities. Subjects were homozygous for F508del-CFTR. Genotyping was performed using a validated CF genotyping test. These criteria were the same in Studies 103 and 104. Even in patients with CF mutations on two alleles, recently published CF consensus recommendations for diagnosis of CF (Farrell PM, White TB, Ren CL et al. 2017) specify that sweat chloride should be at least 30 mmol/L (i.e., sweat chloride testing is necessary to confirm the diagnosis in subjects with two CF-causing mutations) whereas a previous recommendation was that sweat chloride should be above 60 mmol/L. The baseline data on sweat chloride show that values range between 64.5 to 123.0 mmol/L in the placebo group and between 46.0 and 119.0 in the lum/iva group, which is consistent with a CF diagnosis according to the most recent recommendations. Enrolment was limited to subjects with $LCI_{2.5} \geq 7.5$ at the Screening Visit, reflective of uneven ventilation and small airways disease.(Normal value <7.5). Spirometry at baseline (ppFEV1) could be normal (pp FEV1 >70). Subjects with a history of any illness or condition that could confound study results or pose an additional safety risk were excluded. The inclusion and exclusion criteria were considered appropriate by the CHMP.

104 subjects were randomised to receive LUM 200 / IVA 250 mg q12h and 102 subjects to receive placebo-matched control, for a period of 24 weeks. There was an overall low rate of discontinuation that was similar in the LUM/IVA (5.8%) and placebo (5.0%) groups. Patient demographics were overall well balanced between treatment arms for age (at screening, median 9 yrs in both, range 6 – 11yrs), weight and height.

In study 109 there were more females than males (59.3% versus 40.7%), despite males tending to be represented in high numbers than females in all CF age groups. Numbers of males and females were balanced between treatment arms, however females are known to fare worse than males in the clinical course of CF although the survival disadvantage in females is more apparent in the older age groups as one would expect. The vast majority of subjects were white (96.1%).

Baseline disease severity and pulmonary function abnormality were overall balanced between treatment arms. Baseline sweat chloride levels in both groups are compatible with CF. ppFEV1 $\geq$ 70 was an inclusion criterion in study 109 although a few patients had values lower than this, more in the active treatment arm which would have tended to favour placebo.

Study conduct was overall acceptable and there were no protocol deviations likely to have affected the conclusions of the study.

The primary efficacy endpoint was absolute change in $LCI_{2.5}$ from baseline. The primary analysis was a between-group comparison between placebo and active treatments of change from baseline in $LCI_{2.5}$ through 24 weeks.

Study 109 evaluated $LCI_{2.5}$ as the primary endpoint whereas studies 103 and 104 in the 12 years and older population evaluated $ppFEV_1$ as the primary endpoint. Reduction reflects improvement in ventilation homogeneity.

The Report from the Workshop on Endpoints in Cystic Fibrosis clinical trials (EMA/769571/2012) acknowledges that in younger patients with milder disease, and in whom respiratory function as determined by spirometry may not have begun to decline, FEV1 may not be sufficiently sensitive to detect a treatment effect. The report from the workshop recommends instead that in younger patients, a more sensitive endpoint such as LCI should be evaluated, although the limited clinical experience of this as an outcome measure, and the lack of an established clinically relevant magnitude of benefit, are also acknowledged.

Even in the presence of normal spirometry, as is often the case in the younger patients, investigation of potential disease-modifying treatments in CF is encouraged in the hope of slowing disease progression and preventing or delaying permanent lung parenchymal damage in addition to other organ damage such as biliary cirrhosis and pancreatic damage.

$LCI_{2.5}$ is the most commonly used multiple breath washout test (MBW) parameter. $LCI_{2.5}$ measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value. It is a sensitive outcome measure appropriate to this patient population and also more likely to reveal differences in ventilation homogeneity than $LCI_{5.0}$ which measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value. $LCI_{5.0}$ was evaluated as a secondary endpoint. Although LCI is encouraged as an efficacy variable in younger CF patients, there are limited clinical data to validate clinical relevance of an effect.

Secondary efficacy endpoints included analyses of lung function (LCI and spirometry), sweat chloride, nutritional indices (body mass index [BMI], weight, height, and associated z-scores for each), Cystic Fibrosis Questionnaire-Revised [CFQ-R] responses, Treatment Satisfaction Questionnaire for Medication [TSQM] responses, and clinical events related to outcomes (e.g., PExs). Other evaluations included analyses of faecal elastase-1 (FE-1), immunoreactive trypsinogen (IRT), and sputum microbiology. An exploratory evaluation of imaging results was also included.

Efficacy analyses were performed using the Full Analysis Set (FAS). The primary efficacy endpoint, absolute change from baseline in $LCI_{2.5}$ through Week 24, was analysed using a mixed model for repeated measures (MMRM) which made use of all available data even if a subject had missing data at some post-baseline visits. The model included the absolute change in $LCI_{2.5}$ from baseline (including all measurements up to Week 24 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for weight (<25 kg versus ≥ 25 kg) and ppFEV1 severity (<90 versus ≥ 90), both as determined at the Screening Visit, and the baseline LCI2.5 as a continuous variable. Analyses for secondary endpoints 2, 4 through 6, and 12 through 14 were based on an MMRM analysis similar to that used for the primary analysis.

Efficacy data and additional analyses

The primary efficacy endpoint was the absolute change from baseline in $LCI_{2.5}$ from baseline through week 24, active versus placebo comparison of treatment difference. The primary endpoint was met in demonstrating a statistically significant treatment difference for LUM/IVA versus placebo, in favour of LUM/IVA, for the efficacy variable absolute change in $LCI_{2.5}$ from baseline through week 24. There was a LS mean treatment difference of -1.09 (95% CI, -1.43, -0.75) p<0.0001 for the absolute change through Week 24.

The size of the treatment effect appears small. However, there are limited data from trials using this endpoint and a MCID has not yet been defined. Effect sizes in studies have ranged from -1 to -2 depending on the type of intervention and the duration of treatment (Amin 2010, Thorax; Amin 2011, Eur Respir J; Davies 2012, American Thoracic Society International Conference. San Francisco). Limited longitudinal data from the placebo group of interventional trials are available to define whether an intervention exceeds the intrinsic variability of the test. The report from the recent workshop on endpoints in clinical trials nonetheless considers this endpoint sufficiently established for trials in CF patients 6 – 11 years of age.

There was a high percentage of missing data (16.7%) for the absolute change in LCI at week 24. It was clarified that the majority of missing assessments for LCI were missing due to technical unacceptability (fewer than 2 acceptable values) on the evaluation of a blinded adjudicator. At Week 24, 26 subjects had technically unacceptable LCI values compared with 21 – 27 subjects at other visits. The primary analysis was an MMRM analysis that averaged the treatment effect through week 24. A supportive analysis was conducted using an ANCOVA model with missing data imputed which was consistent with the primary analysis.

The LCI and spirometry measurements were calculated centrally without knowledge of preceding values which had been scrambled to maintain blinding. There was an overall low rate of treatment discontinuation that was similar in LUM/IVA and placebo groups.

There were approximately 20% more females than males in study 109, whereas males tend to be more represented in the CF population at large. Subgroup analysis by gender suggests a bigger treatment difference between LUM/IVA and placebo in females than males (LS mean difference -1.23; 95% CI -1.72, -0.73, p < 0.0001 in females; and LS mean difference -0.88, 95% CI -1.33, -0.42, p < 0.0003 in males). The homogeneity of the treatment effect across subgroups (including sex) was evaluated in a mixed-effects model for repeated measures (MMRM) analysis by testing each treatment-by-subgroup interaction in the corresponding model. In Study 109, there were no treatment-by-subgroup interactions that were statistically significant. The lack of a statistically significant treatment by gender interaction (p=0.1654) does not exclude one, given that the test was not powered to reveal an interaction. Although subgroup analysis revealed an apparently greater treatment response in females compared with males, males nonetheless demonstrated a statistically significant improvement in LCI relative to placebo that can be considered clinically relevant.

Secondary efficacy endpoints: Average absolute change in sweat chloride from baseline at Day 15 and at Week 4 was specified in the SAP as one of three key secondary efficacy endpoints. LUM/IVA resulted in improvement (i.e., a reduction) in sweat chloride at Day 15 and sustained through Week 24, with a LS mean treatment difference of -20.8 mmol/L (95% CI -23.4, -18.2; P<0.0001) for the average absolute change at Day 15 and at Week 4. There is no discussion in the SAP of a pre-specified hierarchy for the

secondary efficacy endpoints and therefore statistical significance is regarded as nominal for all secondary endpoints.

The reduction in sweat chloride is consistent with restoration of the biochemical defect and with the combined corrector/potentiator action of LUM/IVA. Although the mean reduction of ~ 20 mmol/L was quite rapid and marked, the decline levelled off with no evidence of ongoing decline. The decline in mean sweat chloride to ~ 80 mmol/L is still substantially higher than normal range for sweat chloride (< 30 mmol/L). References were provided to support, from natural history data, that improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit. It is clarified that no patients achieved normalisation of sweat chloride.

There was a trend to improvement in BMI in favour of LUM/IVA but it is difficult to assess whether this reflects improved nutritional status from improved pancreatic function, without additional supportive evidence. At baseline, mean age- and sex-adjusted nutritional indices were -0.21 (weight-for-age z-score), -0.14 (BMI-for-age z-score), and -0.14 (height-for-age z-score), reflecting that some patients were under-nourished at study entry and who may be more sensitive to revelation of increase in BMI due to improved nutritional status. Although the absolute change from baseline BMI in subjects with a BMI z-score <0 was similar in the LUM/IVA and placebo groups over 24 weeks of treatment, responder analysis in subjects with a BMI z-score <0 showed that the percentage with a BMI value ≥ 50th percentile at Week 24 was higher in the LUM/IVA group (9 [14.8%] subjects) than in the placebo group (4 [7.7%] subjects). This supports that LUM/IVA has a positive effect on nutritional parameters in undernourished children.

There was a numerical improvement in CFQ-R respiratory domain score through Week 24 with a treatment difference compared to placebo of 2.5 points which is less than the MCID of 4 points in patients 14 years and older. Given that the patient population was at a relatively early stage of disease, patient reported outcome such as this would be relatively insensitive to detect a treatment benefit and therefore although this is a validated PRO in CF, the lack of clear benefit over placebo is not considered to be of major concern.

Of the three key secondary efficacy endpoints, only one (sweat chloride) demonstrated a statistically significant (nominal) difference for LUM/IVA versus placebo but the clinical relevance of this magnitude of reduction is unclear. The other key secondary efficacy endpoints were consistent with a trend to improvement, recognising that definitive efficacy improvement is difficult to demonstrate in a patient population with relatively mild disease at baseline. Although study 011B arguably more clearly demonstrated clinically relevant change from baseline across secondary efficacy endpoints, the patients had more impaired respiratory function at baseline and may as a population have been more sensitive to revelation of benefit over a relatively short time scale. Study 011B was uncontrolled but provides some support for clinical relevance of efficacy benefit. The documented efficacy benefit for LUM/IVA in 12 years and older patients, albeit in a different posology, is also supportive.

The $ppFEV_1$ was evaluated as a supportive secondary efficacy endpoint in study 109 for the reasons outlined i.e. the 6 – 11 year old population is likely to be relatively insensitive to revelation of benefit when baseline spirometry is frequently normal. Nonetheless, in study 011B patients had lower baseline $ppFEV_1$ compared to study 109 and in study 011B, there was some evidence of improvement in $ppFEV_1$ at week 24 suggesting the potential for some reversal of lung function deficit.

The possibility of improvement in pulmonary architecture by lung imaging in patients with normal spirometry can be further explored, i.e. in a small number of subjects in study 109 exploratory lung imaging was performed. There was evidence of reduced bronchiectasis, mucous plugging, peribronchial

thickening, and hyperinflation based on CT and reduced bronchiectasis, mucous plugging, and peribronchial thickening based on UTE MRI although the numbers are too small to draw definitive conclusions. Nonetheless, this provides some support that the trend to improvement in $ppFEV_1$ by 24 weeks may reflect potential for improvement as well as slowing of disease progression. Exploratory pulmonary imaging will be continued as a substudy in the long term study 110 in 6 – 11 year olds. If beneficial effect on pulmonary architecture can be confirmed, this would support introduction of correction therapy at earlier stages of disease.

2.5.4. Conclusions on the clinical efficacy

Overall, the CHMP considered that clinical efficacy has been sufficiently demonstrated in CF patients homozygous for *F509del-CFTR* aged 6 – 11 years administered with the new FDC combination of Orkambi at the proposed posology.

2.6. Clinical safety

Patient exposure

Study 109: 204 subjects were exposed to study drug, 193 (94.6%) subjects completed treatment, and 196 (96.1%) subjects completed the study. The treatment discontinuation rate was similar in the LUM/IVA (5.8%) and placebo (5.0%) groups. Overall, the most common reason for treatment discontinuation was an AE (2.5%). The treatment discontinuation rate due to AE was similar in the LUM/IVA (2.9%) and placebo (2.0%) groups. The overall mean exposure duration was 161.7 days, and the majority of subjects (95.6%) received >16 weeks of study drug exposure. The mean exposure duration was similar in the LUM/IVA (160.1 days) and placebo (163.3 days) groups.

Studies 011B and 110: In Study 011B, 58 subjects were enrolled and exposed to study drug. A total of 54 (93.1%) subjects completed treatment. In the Study 110 Cumulative Study Period, 58 subjects received at least 1 dose of study drug, and the mean exposure was 438.6 days (62.7 weeks). A total of 28 (48.3%) subjects received ≥ 48 to <72 weeks of treatment, and 21 (36.2%) subjects received ≥ 72 to <96 weeks of treatment.

Adverse events

Treatment-emergent adverse events

TEAEs were defined as any AE that increased in severity or that developed upon or after the initial dosing of study drug to 28 days after the last dose of study drug (referred to as AEs).

Study 109: A total of 81 (39.7%) subjects had at least 1 AE considered related to the study drug (related [0.5%] or possibly related [39.2%], as determined by the investigator). The majority of subjects had AEs that were considered mild (87 [42.6%] subjects) or moderate (98 [48.0%] subjects) in severity. Eleven (5.4%) subjects had AEs that were severe. No life-threatening AEs occurred. Twelve (5.9%) subjects had AEs that led to treatment interruption (9 [8.7%] subjects in the LUM/IVA group and 3 [3.0%] subjects in

the placebo group). A total of 5 (2.5%) subjects had AEs that led to treatment discontinuation (3 [2.9%] subjects in the LUM/IVA group and 2 [2.0%] subjects in the placebo group). A total of 24 (11.8%) subjects had serious adverse events (SAEs) (13 [12.6%] subjects in the LUM/IVA group and 11 [10.9%] subjects in the placebo group), 5 of whom had an SAE considered related to study drug (2 [1.9%] subjects in the LUM/IVA group and 3 [3.0%] subjects in the placebo group). No subjects had an AE with an outcome of death.

Studies 011B and 110: During the Cumulative Study Period, 56 (96.6%) subjects had at least 1 AE, the majority of who had AEs that were considered mild (24.1%) or moderate (62.1%) in severity. Ten (17.2%) subjects had at least 1 SAE. No subjects had an AE that led to death. Across AE categories, the exposure-adjusted numbers of events were generally similar or lower in the Study 110 Period than during the initial 24 weeks of treatment in Study 011B.

Common adverse events

Study 109: AEs with a frequency of ≥ 5% at the preferred term (PT) level in any treatment group are summarized by system organ class (SOC) and PT. The most common AEs (≥ 10% incidence overall at the PT level) were cough, infective PEx of CF, pyrexia, nasal congestion, oropharyngeal pain, productive cough, upper respiratory tract infection, and headache. Overall, the AEs were mostly consistent with common manifestations of CF disease. The AEs that occurred more frequently (≥ 5 percentage points) in the LUM/IVA group versus the placebo group were productive cough (11.6 percentage points higher), sputum increased (8.7 percentage points higher), nasal congestion (8.6 percentage points higher), and upper abdominal pain (5.7 percentage points higher). The incidence of pyrexia was 5.2 percentage points higher in the placebo group than the LUM/IVA group.

Studies 011B and 110: During the Cumulative Study Period, the most common AEs (incidence of ≥ 20%) were cough (60.3%), infective PEx of CF (39.7%), nasal congestion (36.2%), headache (25.9%), pyrexia (24.1%), abdominal pain upper (22.4%), and rhinorrhoea (20.7%). The exposure-adjusted numbers of AEs were generally similar or lower in the Study 110 Period than during the initial 24 weeks of treatment in Study 011B.

Adverse events over time

Study 109: A total of 176 (86.3%) subjects had onset of their first AE within the first 8 weeks of treatment. The incidence of AEs was highest in the first 8 weeks, and subsequently decreased; a similar trend was noted in both the placebo and LUM/IVA groups.

Studies 011B and 110: In Study 011B, the incidence of AEs was highest in the first 8 weeks, and subsequently decreased.

Serious adverse event / deaths / other significant events

Study 109: A total of 24 (11.8%) subjects had at least 1 serious adverse event (SAE). The percentage of subjects with any SAEs was similar in the LUM/IVA (12.6%) and placebo (10.9%) groups. The only SAE that occurred in >2 (1.0%) subjects overall by PT was infective PEx of CF, a common manifestation of CF disease, which occurred in 8 (7.8%) subjects in the LUM/IVA group and 5 (5.0%) subjects in the placebo group.

Studies 011B and 110: During the Cumulative Study Period, the overall percentage of subjects with at least 1 SAE was 17.2%. By PT, the most common SAE was infective PEx of CF, which occurred in 7 (12.1%) subjects. All other SAEs occurred in 1 subject each.

The overall exposure-adjusted numbers of SAEs were similar in the Study 110 and Study 011B periods. The majority of SAEs by PT occurred in only 1 subject, without any trend or pattern. There were no deaths.

Adverse events of special interest (AESI)

Before database lock, AESIs were identified to evaluate specific events of interest by grouping AE terms that represent similar medical concepts, from the same or different SOC. The AESIs were defined as AEs related to elevated transaminases, respiratory symptoms, and respiratory events. In the initial marketing application for use of Orkambi in patients 12 years of age and older, the same AESIs were identified and analysed.

Respiratory system – respiratory symptoms or reactive airways

AESIs were created for 3 specific respiratory symptoms (PTs: chest discomfort, dyspnoea, and respiration abnormal) and a larger grouping of respiratory events, the latter of which includes the 3 specific respiratory symptoms events and 4 reactive airway events (PTs: asthma, bronchial hyper-reactivity, bronchospasm, and wheezing).

Study 109: A total of 32 (15.7%) subjects had AESIs of respiratory events. The percentage of subjects with AESIs of respiratory events was 18.4% in the LUM/IVA group versus 12.9% in the placebo group. Twenty (9.8%) subjects overall had AESIs of respiratory symptoms. By PT, chest discomfort occurred in 1 (0.5%) subject, dyspnoea occurred in 10 (4.9%) subjects, and respiration abnormal occurred in 10 (4.9%) subjects. For each PT, the incidence was similar in the LUM/IVA and placebo groups. Other respiratory events of asthma occurred in 4 (3.9%) subjects in the LUM/IVA group and 1 (1.0%) subject in the placebo group, and wheezing occurred in 5 (4.9%) subjects in the LUM/IVA group and 3 (3.0%) subjects in the placebo group. All AESIs of respiratory events were mild (25 of 32 subjects) or moderate (7 of 32 subjects) in severity. One (1.0%) subject in the LUM/IVA group had AESIs of respiratory events (PT: respiration abnormal) that led to interruption and discontinuation of treatment. No subject had a serious AESI of respiratory events.

Among the 32 subjects with AESIs of respiratory events, the median (range) time-to-onset of the first AESI was 17.0 (1 to 144) days in the LUM/IVA group and 10.0 (1 to 159) days in the placebo group. The median (range) event duration was 8.5 (1 to 169) days in the LUM/IVA group and 3.0 (1 to 45) days in the placebo group.

Subgroup Analysis: Subjects with a ppFEV1 of <90 at baseline had incidences of 21.2% (LUM/IVA group) and 12.5% (placebo group) for AESIs of respiratory events. Subjects with a ppFEV1 of ≥ 90 at baseline had incidences of 16.0% (LUM/IVA group) and 13.2% (placebo group) for AESIs of respiratory events.

Studies 011B and 110: During the Cumulative Study Period, the percentage of subjects with AESIs of respiratory events was 12.1% overall, 6.9% for wheezing, 3.4% for dyspnea and respiration abnormal, and 1.7% for bronchial hyperreactivity. All events were mild or moderate in severity. None were severe, life-threatening, led to death, or led to LUM/IVA treatment discontinuation or interruption.

Across PTs and descriptive categories (e.g., SAEs), the exposure-adjusted numbers of events were either lower or similar in the Study 110 Period than in the initial 24 weeks of treatment in Study 011B.

The median (range) time-to-onset of first AESI of respiratory events was 100 (1 to 242) days. The median (range) event duration was 2 (1 to 29) days.

Subgroup Analysis: During the Cumulative Study Period, subjects with a ppFEV1 of <90 percentage points at baseline had an incidence of 11.1% for AESIs of respiratory events and subjects with a ppFEV1 of ≥ 90 percentage points at baseline had a similar incidence of 13.3%.

Spirometry: Serial spirometry assessments on Day 1, Day 15, Week 16, and Week 24 were obtained for a subset of subjects with the objective of evaluating post-dose FEV1 because of the transient decline in ppFEV1 that has been observed with LUM/IVA treatment in older patients.

On Day 1, the mean (range) absolute change in $ppFEV_1$ 4 to 6 hours after the first dose was -7.7 (-24.0, 12.8) percentage points in the LUM/IVA group and -1.4 (-33.9, 17.5) percentage points in the placebo group. The number and percentage of subjects with AESIs of respiratory events on Day 1 was 3 (2.9%) subjects in the LUM/IVA group versus 4 (4.0%) subjects in the placebo group. On Day 15, the mean (range) absolute change in $ppFEV_1$ 4 to 6 hours after dosing was -1.3 (-25.2, 17.8) percentage points in the LUM/IVA group and 0.1 (-19.8, 17.2) percentage points in the placebo group, demonstrating a marked attenuation in the post-dose decline in $ppFEV_1$. This post-dose decline resolved at Week 16, with a mean (range) absolute change in $ppFEV_1$ 4 to 6 hours after dosing of 0.5 (-16.2, 22.1) percentage points in the LUM/IVA group and 0.6 (-25.9, 11.3) percentage points in the placebo group. The observed post-dose decline in mean $ppFEV_1$ for the LUM/IVA group at 4 to 6 hours after dosing at Week 24 (absolute mean change [range] = -2.8 [-11.7, 10.0] percentage points in the LUM/IVA group and 0.1 [-7.8, 8.0] percentage points in the placebo group) most likely represents variability in the data rather than a clinically meaningful effect given the relatively small sample size. Overall, the serial spirometry data demonstrated a short-term, post-dose decline in $ppFEV_1$ that was generally asymptomatic with relatively few respiratory AEs observed on Day 1, and was markedly attenuated by Day 15 and resolved by Week 16.

A total of 5 (4.9%) subjects in the LUM/IVA group and 5 (5.0%) subjects in the placebo group had AEs of FEV1 decreased, and 2 (1.9%) subjects in the LUM/IVA group and 3 (3.0%) subjects in the placebo group had AEs of pulmonary function test decreased. These AEs were mild to moderate in severity and none were considered serious or required interruption or discontinuation of study drug treatment.

Laboratory findings

Study 109: AESIs of elevated transaminases occurred in 20 (9.8%) subjects. The percentage of subjects with AESIs of elevated transaminases was similar in the LUM/IVA (9.7%) and placebo (9.9%) groups. By PT, ALT increased occurred in 17 (8.3%) subjects, AST increased occurred in 13 (6.4%) subjects, and transaminases increased occurred in 3 (1.5%) subjects. The percentage of subjects was similar in the LUM/IVA and placebo groups for each PT. The majority of AESIs of elevated transaminases were mild (8 of 20 subjects) or moderate (9 of 20 subjects) in severity. One subject in the LUM/IVA group and 2 subjects in the placebo group had AESIs of elevated transaminases that were severe. No life-threatening AESIs of elevated transaminases occurred. Three (1.5%) subjects, all of whom were in the LUM/IVA group, had AESIs of elevated transaminases that led to treatment interruption. Four (2.0%) subjects (2 subjects in the LUM/IVA group and 2 subjects in the placebo group) discontinued treatment due to an AESI of

elevated transaminases; with 1 exception, the events were mild to moderate in severity and all were considered possibly related to study drug and resolved. Two (1.0%) subjects, both of whom were in the placebo group, had serious AESIs of elevated transaminases; the events were moderate to severe in severity, considered possibly related to study drug, and resolved. Among the 20 subjects with AESIs of elevated transaminases, the median (range) time-to-onset of the first AESI was 85.0 (22 to 150) days in the LUM/IVA group and 59.0 (16 to 169) days in the placebo group. The median (range) event duration was 14.0 (3 to 65) days in the LUM/IVA group and 20.0 (8 to 92) days in the placebo group.

Studies 011B and 110: During the Cumulative Study Period, the percentage of subjects with elevated transaminase AESIs was 15.5% overall, 15.5% for ALT increased, and 8.6% for AST increased. None of the events were severe, life-threatening, or led to death. One (1.7%) subject had an event that led to treatment discontinuation; this occurred during the initial 24 weeks of treatment in Study 011B. Four (6.9%) subjects had an event that led to treatment interruption; for 3 subjects, this occurred during the initial 24 weeks of treatment in Study 011B. One (1.7%) subject had an event that was considered an SAE; this occurred during the initial 24 weeks of treatment in Study 011B. Across PTs and descriptive categories (e.g., SAEs), the exposure-adjusted numbers of events were lower in the Study 110 Period than in the initial 24 weeks of treatment in Study 011B. The median (range) time-to-onset of first AESI of elevated transaminases was 85 (10 to 225) days. The median (range) event duration was 25.5 (7 to 282) days.

Safety in special populations

The AEs were summarized by subgroups of ppFEV1 severity, weight, sex, geographic region, and prior use of inhaled antibiotics or bronchodilators for Study 109 and by ppFEV1 severity, sex, and age for Study 011B. Some numerical differences were observed; however, there were no trends that suggested a different safety profile in any of the subgroups. In Study 110, subgroup analyses based on ppFEV1 at baseline were performed for the respiratory AESIs only.

Safety related to drug-drug interactions and other interactions

No additional interactions are expected in this subpopulation in comparison with the currently identified ones.

Discontinuation due to adverse events

A total of 5 (2.5%) subjects had AEs that led to treatment discontinuation. The incidence was similar in both groups: 3 (2.9%) subjects in the LUM/IVA group and 2 (2.0%) subjects in the placebo group. By PT, ALT increased, AST increased, and transaminases increased each occurred in 1 (1.0%) subject in the LUM/IVA group and 1 (1.0%) subject in the placebo group, and respiration abnormal occurred in 1 (1.0%) subject in the LUM/IVA group. A total of 12 (5.9%) subjects had AEs that led to treatment interruption; 9 (8.7%) subjects in the LUM/IVA group and 3 (3.0%) subjects in the placebo group. By PT, ALT increased, AST increased, and rash occurred in 2 (1.9%) subjects each in the LUM/IVA group. All other AEs that led to treatment interruption occurred in 1 subject each.

Post marketing experience

LUM/IVA (Orkambi, 200-mg/125-mg tablets) was first approved in the US on 02 July 2015, followed by EU Marketing Authorisation granted on 19 November 2015 via the centralised procedure. Additionally, Orkambi is approved for marketing in Canada, Australia, Switzerland, and Israel. LUM/IVA (100-mg/125-mg tablets) was approved in the US for patients 6 to 11 years of age on 28 September 2016.

Since the initial approval, it is estimated that 9838 patients (representing 6008-years) have been treated with commercial LUM/IVA cumulatively up to the data lock point (19 November 2016) of the second periodic safety update report (PSUR 2). The post-marketing safety data are summarized in the 2 completed PSURs. PSUR 2 was submitted on 27 January 2017 and is currently under assessment. The benefit-risk profile of LUM/IVA treatment remains favourable.

2.6.1. Discussion on clinical safety

Data from the 24-week, placebo-controlled study 109 and uncontrolled study 011B showed that administration of LUM/IVA was overall safe and well tolerated for up to 24 weeks in subjects 6 through 11 years of age. The common AEs observed were mostly manifestations of CF disease. No new safety concerns were identified compared with subjects aged 12 years and older.

A total of 32 (15.7%) subjects had AESIs of respiratory events in Study 109, all of which were mild or moderate in severity. The percentage of subjects with AESIs of respiratory events was 18.4% in the LUM/IVA group versus 12.9% in the placebo group; these percentages are lower than what was observed in subjects 12 years of age and older (Studies 103 and 104, in which 26.3% of subjects on active treatment had AESIs of respiratory events), suggesting a better respiratory tolerability in young patients with more preserved lung function. Only 1 (1.0%) subject in the LUM/IVA group had AESIs of respiratory events that led to interruption and discontinuation of treatment.

Serial spirometry assessments on Day 1, Day 15, Week 16, and Week 24 of Study 109 were obtained for a subset of subjects with the objective of evaluating postdose FEV1 due to concerns raised over observations of initial transient decline in FEV1 on initiation of treatment in older patients, with the added concern that this may be greater in younger children with smaller diameter airways. Serial spirometry data demonstrated a transient decline (at 4 – 6 hours post-dose) in ppFEV1 that was generally asymptomatic. Although the mean decline of -7.7 in LUM/IVA patients could be considered potentially clinically significant whereas the mean decline was -1.4 in placebo patients, there was also extremely wide variability (95% CI -24.8, 12.8 in LUM/IVA versus -33.9, 17.5 in placebo). Therefore, some placebo treated patients apparently declined more than LUM/IVA patients and the variability may in part reflect the greater unreliability of spirometry measurements that require voluntary effort in young children. Respiratory AESI on Day 1 were 2.9% in LUM/IVA and 4.0% in the placebo group consistent with the asymptomatic nature of the decline. Thus, the decline in FEV1 does not appear to be associated with respiratory adverse events at the time. The decline was markedly attenuated by Day 15 and resolved by Week 16. There was also an overall low rate of treatment discontinuation in studies 011 and 109 that was similar in LUM/IVA and placebo groups which supports that the observation of decline in ppFEV1, is not of major concern.

Literature data provide external evidence of a transient, post-dose decline in FEV1, the mechanism being unknown. Data support that the effect is similar in the 6 -11 years age group compared to older patients. More than 80% of patients in the Orkambi studies were already using bronchodilators at study entry which is reflective of use in the CF population at large. Subgroup analysis (subjects with or without

bronchodilator use) did not demonstrate any trend suggesting a lower rate of respiratory events in subjects with bronchodilator use. Published studies have examined bronchodilator use as risk minimisation upon initiation of LUM/IVA, with mixed success. Overall therefore there does appear to be insufficient evidence to support additional bronchodilator use or other risk minimisation strategy to cover the initiation of treatment with Orkambi. Furthermore, most patients will have been prescribed bronchodilators. The SmPC has been updated with the information on the temporary FEV1 decline at the start of the treatment with Orkambi.

In the uncontrolled study 011B and in study 109, ALT and AST elevations appeared to be higher than that observed in subjects 12 years of age and older (studies 103 and 104). These observations are consistent with information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults, and are also consistent with a background rate of 15.3% (ALT/AST >3 × ULN) in placebo-treated subjects of the same age group from a previously completed 24-week IVA monotherapy study (Study VX08-770-103 Part B). In study 109 (24 week placebo-controlled study in 204 patients 6 – 11 years, the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 1.0%, 4.9% and 12.6% respectively in the LUM/IVA treated patients and 2.0%, 3.0% and 7.9% in the placebo treated patients. This illustrates that transaminase elevation is a feature of the disease. No patients had total bilirubin levels > 2 x ULN. There were ~5% more patients with modestly elevated (>3 x ULN) transaminases in the LUM/IVA group. No difference was observed for ALT/AST >5 and 8 × ULN, as well as discontinuations, between the LUM/IVA and placebo groups, and the only SAEs occurred in 2 subjects in the placebo group.

The Cumulative Study Period, which included the Study 011B and Study110 periods, covered approximately 60 weeks of LUM/IVA exposure in 49 subjects. As would be expected, cumulative incidence rates (15.5% overall), of transaminase elevation were higher than in the shorter duration studies. No events of transaminase elevation were severe. The cumulative study period was an uncontrolled, open label study period in which the contribution from longer disease duration versus longer drug exposure cannot be distinguished. However, the published literature also indicates that transaminase elevation is more common in younger patients with CF than in adults.

There were no cases of possible drug-related liver toxicity sufficient to satisfy Hy's law. An association between Orkambi and drug induced liver injury cannot be excluded, however, as stated in section 4.4 of the SmPC. Because of this, section 4.4 includes the recommendation that liver function should be assessed prior to initiation of Orkambi, every 3 months during the first year of treatment and annually thereafter, with more frequent monitoring in patients with a history of elevations in ALT, AST or bilirubin. In the event of significant elevation of ALT or AST, with or without elevated bilirubin (either ALT or AST >5 x the upper limit of normal [ULN], or ALT or AST >3 x ULN with bilirubin >2 x ULN), dosing with lumacaftor/ivacaftor should be discontinued and laboratory tests closely followed until the abnormalities resolve. Following resolution of transaminase elevations, the benefits and risks of resuming dosing should be considered.

Although transaminases are generally higher in younger patients with CF, for reasons that are unclear, there is no evidence that Orkambi poses a higher risk of serious drug-related toxicity in the 6 – 11 year old age group, provided they are administered with the age-appropriate formulation. Following administration of the respective age appropriate formulations for 6 – 11 year old and 12 years and older patients, LUM and IVA exposures in most 6 – 11 year old patients lie within the 5th and 95th percentiles of exposures in the older patients. The current warnings in section 4.4 of the SmPC are therefore considered adequate for the line extension.

Safety data from Study 110 showed that administration of LUM/IVA was overall well tolerated in subjects 6 years of age and older for up to 60 weeks (24 weeks in Study 011B and 36 weeks in Study 110) without new safety concerns.

Blood Pressure data across Studies 109, 011B, and 110 showed that BP levels were variable but generally consistent with previous observations from the LUM/IVA-treated subjects 12 years of age and older (Studies 103 and 104).

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

2.6.2. Conclusions on the clinical safety

Overall, the findings from Study 109, as well as Studies 011B and 110, support the use of LUM/IVA in subjects 6 through 11 years of age with CF, homozygous for F508del. The safety outcomes were generally consistent with the background profile in patients with CF and the established safety profile of LUM/IVA.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 19 November 2017.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Respiratory events • Blood pressure increase
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 6 years of age or in patients who are not homozygous for *F508del-CFTR* mutation
Missing information	• Use in pregnant and lactating women • Patients with ppFEV$_1$ <40 • Long-term safety • Safety in patients with cardiac diseases • Use in patients with organ transplant • Clinical relevance of heart rate decrease

	• Effect of LUM/IVA on P-gp substrates • Clinical relevance of interaction potential between transporters and lumacaftor and/or ivacaftor • Potential environmental risk

CFTR: cystic fibrosis transmembrane conductance regulator; CYP3A: cytochrome P450 - enzyme subfamily 3A; LUM/IVA: lumacaftor in combination with ivacaftor; P-gp: permeability glycoprotein; $ppFEV_1$: forced expiratory volume in 1 second

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, 3) 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 • Blood pressure increase • 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 $ppFEV_1$ <40 • Long-term safety • Safety in patients with cardiac diseases • Clinical relevance of heart rate decrease	Started	Final Report: December 2016

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 106 (interventional, 3) 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 • Blood pressure increase • 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 $ppFEV_1$ <40 • Safety in patients with cardiac diseases • Clinical relevance of heart rate decrease	Started	Final Report: March 2017
Study 110 (interventional, 3) A Phase 3 Rollover Study to Evaluate the Safety and Efficacy of Long-Term Treatment With LUM/IVA in Subjects Aged 6 Years and Older With CF, Homozygous for the *F508del-CFTR* Mutation	To evaluate the long-term safety and efficacy of LUM/IVA in subjects aged 6 years and older with CF	• Respiratory events • Blood pressure increase • Hepatobiliary events • Cataracts • Cardiac arrhythmias • Long-term safety • Clinical relevance of heart rate decrease	Started	Final Report: August 2019

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 108 (PASS) (non-interventional, 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	• Blood pressure increase (recorded in registries as "hypertension") • Hepatobiliary events • Cardiac arrhythmias • Off-label use • Use in pregnant women • Patients with $ppFEV_1$ <40 • Long-term safety • Safety in patients with cardiac diseases • Use in patients with organ transplant	Started	Annual Reports: December 2017/2018/2019/ 2020 Final Report: December 2021
Nonclinical, 3	Nonclinical studies to evaluate potential environmental risk for lumacaftor and ivacaftor	• Potential environmental risk	Ongoing	Final ERA Reports: May 2017

CF: cystic fibrosis; CYP: cytochrome P450; ERA: environmental risk assessment; LUM/IVA: lumacaftor in combination with ivacaftor; PASS: Post-authorisation Safety Study; $ppFEV_1$: percent predicted forced expiratory volume in 1 second;

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 $ppFEV_1$ <40 is recommended. **Section 4.8** describes respiratory events as an adverse reaction and described that these events are	Not applicable

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	more common in patients with lower ppFEV$_1$. Section 4.8 also describes the short-term effect of postdose ppFEV$_1$ decline.	
Blood pressure increase	**Section 4.4** describes warnings of increased blood pressure during Orkambi therapy and recommends periodic blood pressure monitoring. **Section 4.8** describes hypertension events as adverse reactions.	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	Not applicable

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	patients are provided. **Section 5.3** summarizes preclinical data relevant to this potential risk. Prescription-only medicine.	
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 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
Off-label use in children less than 6 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 6 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

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Patients with ppFEV$_1$ <40	**Section 4.4** states that additional monitoring is recommended in patients with ppFEV$_1$ <40 during initiation of therapy. **Section 4.8** describes the higher incidence of respiratory events in patients with lower pre-treatment ppFEV$_1$. **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
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
Clinical relevance of heart rate decrease	**Section 5.1** describes clinical data on the pharmacodynamic effect of Orkambi to decrease heart rate. 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

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Clinical relevance of interaction potential between transporters and lumacaftor and/or ivacaftor	**Section 4.5** describes the potential for LUM/IVA to interact with transporters. Lumacaftor is a substrate for BCRP; co-administration of Orkambi with medicinal products that inhibit BCRP may increase plasma lumacaftor concentration. Lumacaftor inhibits OAT1 and OAT3, and lumacaftor and ivacaftor are inhibitors of BCRP. Coadministration of Orkambi with medicinal products that are substrates of OAT1/3 and BCRP may increase the plasma concentration of such products. **Section 5.2** states that in vitro studies indicate that lumacaftor is a substrate of BCRP. 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; BCRP: breast cancer resistance protein; CYP3A: cytochrome P450 - enzyme subfamily 3A4; hERG: human ether-à-go-go-related gene; LUM/IVA: lumacaftor in combination with ivacaftor; OAT: organic anion transporter; PK: pharmacokinetic; $ppFEV_1$: forced expiratory volume in 1 second

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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.

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 MAH 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 is a medicinal product authorised in the EU that contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU, and as it has an imposed PASS.

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

3.1. Therapeutic Context

3.1.1. Disease or condition

This line extension application is for an extension of indication to children 6 years and older, from the currently approved target population of cystic fibrosis patients 12 years and older, homozygous for F508del-CFTR. Orkambi is authorised in the EU as a single strength LUM 200-mg/IVA 125-mg FDC tablet for oral administration, given as 2 tablets (administered dose LUM 400 mg/IVA 250 mg) every 12 hours. The line extension adds a lower strength FDC tablet, with a different ratio of LUM to IVA (LUM 100-mg/IVA 125-mg) from the existing strength (LUM 200-mg/IVA 125-mg) to be administered as 2 tablets every 12 hours in CF patients 6 to 11 years of age with the F508del CF mutation. The total daily administered dose of LUM is therefore half (400 mg) that of the daily dose in children 12 years and older (800 mg) whereas the daily dose of IVA is the same (500 mg) in both age groups. The aim of therapy is to modify the course of the disease due to correction/improvement in chloride channel function.

3.1.2. Available therapies and unmet medical need

Lumacaftor (a CFTR corrector) has been developed in combination with ivacaftor (a CFTR potentiator) as a fixed dose combination tablet for oral administration in the treatment of CF patients homozygous for the F508del-CFTR mutation. This genotype is present in ~40% of the CF population and results in a severe form of the disease that requires the combined action of lumacaftor to correct processing and trafficking of the CFTR conductance channel, with the potentiator action of ivacaftor to enhance channel open probability. The FDC is currently authorised in the EU as Orkambi, for the 12 years and older population

only. Ivacaftor is authorised as Kalydeco as monotherapy treatment for 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. Orkambi is currently authorised for CF patients 12 years and older homozygous for F508del-CFTR. Lumacaftor and ivacaftor target the biochemical defect in the chloride channel protein whereas all other current treatments for CF alleviate the clinical manifestations of the disease but do not act on the underlying chloride channel defect. Current treatments include inhaled mucolytics, bronchodilators, antibiotics, anti-inflammatory medicines, and pancreatic enzymes.

The new dose combination of Orkambi submitted with the line extension will fulfil an unmet need in the extended target population 6 – 11 years.

3.1.3. Main clinical studies

The pivotal efficacy and safety study 109 was a randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in CF patients aged 6 - 11 years, homozygous for the F508del-CFTR mutation. Subjects were 6 – 11 years old, males and females, confirmed to be homozygous for F508del-CFTR. Patients had evidence of uneven ventilation due to small airways disease at screening (LCI 2.5 ≥ 7.5) but could have normal spirometry (pp FEV1 >70). This is characteristic of this patient population.

3.2. Favourable effects

The primary endpoint in the pivotal trial was met in demonstrating a statistically significant treatment difference for LUM/IVA versus placebo, in favour of LUM/IVA, for the efficacy variable absolute change in LCI2.5 from baseline through week 24. There was a LS mean treatment difference of -1.09 (95% CI, -1.43, -0.75) p<0.0001 for the absolute change through Week 24. Average absolute change in sweat chloride from baseline at Day 15 and at Week 4 was specified in the SAP as one of three key secondary efficacy endpoints. LUM/IVA resulted in improvement (i.e., a reduction) in sweat chloride at Day 15 and sustained through Week 24, with a LS mean treatment difference of -20.8 mmol/L (95% CI -23.4, -18.2; P<0.0001) for the average absolute change at Day 15 and at Week 4. The reduction in sweat chloride is consistent with at least partial restoration of the biochemical defect and with the combined corrector/potentiator action of LUM/IVA.

There was a numerical improvement in CFQ-R respiratory domain score through Week 24 with a treatment difference compared to placebo of 2.5 points. Analysis of ppFEV1 demonstrated a small overall increase from baseline in ppFEV1 by week 24 although there was variability at earlier times. MMRM analysis through week 24 demonstrated a nominal statistically significant difference for LUM/IVA versus placebo in study 109.

In a small number of subjects in study 109 exploratory lung imaging was performed. There was evidence of reduced bronchiectasis, mucous plugging, peribronchial thickening, and hyperinflation based on CT and reduced bronchiectasis, mucous plugging, and peribronchial thickening based on UTE MRI. The numbers are too small to draw definitive conclusions but may reflect potential for improvement in baseline disease as well as slowing of disease progression. Exploratory pulmonary imaging will be continued as a substudy in the long term study 110 in 6 – 11 year olds. If beneficial effect on pulmonary architecture can be confirmed, this would support introduction of correction therapy at early stages of disease to provide pre-

emptive benefit.

3.3. Uncertainties and limitations about favourable effects

The primary efficacy endpoint (absolute change in LCI2.5 from baseline through week 24) reveals LS mean treatment difference for active versus placebo -1.09 (95% CI, -1.43, -0.75). There are limited data from trials using this endpoint and a minimum clinically important difference has not yet been defined. Effect sizes in studies have ranged from -1 to -2 depending on the type of intervention and the duration of treatment (Amin 2010, Thorax; Amin 2011, Eur Respir J; Davies 2012, American Thoracic Society International Conference. San Francisco). Limited longitudinal data from the placebo group of interventional trials are available to define whether an intervention exceeds the intrinsic variability of the test. The report from the recent workshop on endpoints in clinical trials nonetheless considers this endpoint sufficiently established for trials in CF patients 6 – 11 years of age.

The reduction in sweat chloride is consistent with at least partial restoration of the biochemical defect and with the combined corrector/potentiator action of LUM/IVA. Although the mean reduction of ~ 20 mmol/L was quite rapid and marked, the decline levelled off with no evidence of ongoing decline. The decline in mean sweat chloride to ~ 80 mmol/L is still substantially higher than normal range for sweat chloride (< 30 mmol/L). The applicant provided references from natural history data to justify that improvement in CFTR function by 10-20%, in patients homozygous for F508del, would be expected to result in clinically meaningful benefit. It is clarified that no patients achieved normalisation of sweat chloride.

MMRM analysis of change from baseline in ppFEV1 through week 24 in ppFEV1 overall demonstrated an improvement from baseline with LUM/IVA, with nominally significant benefit over placebo. However, there was variability at earlier times and in study 109, there was an early post-dose but transient and asymptomatic decline in ppFEV1. This is discussed further under unfavourable effects.

Of the three key secondary efficacy endpoints, only one (sweat chloride) demonstrated a statistically significant nominal difference for LUM/IVA versus placebo and the clinical relevance of this magnitude of reduction is unclear. The other key secondary efficacy endpoints BMI and CFR-Q failed to demonstrate clear benefit over placebo. However, efficacy benefit reflective of more global clinical improvement is difficult to demonstrate over a short time period in a patient population with relatively mild disease at baseline.

Although the absolute change from baseline BMI in subjects with a BMI z-score <0 was similar in the LUM/IVA and placebo groups over 24 weeks of treatment, responder analysis in subjects with a BMI z-score <0 showed that the percentage with a BMI value ≥ 50th percentile at Week 24 was higher in the LUM/IVA group (9 [14.8%] subjects) than in the placebo group (4 [7.7%] subjects). This supports that LUM/IVA has a positive effect on nutritional parameters in undernourished children.

Study 011B arguably more clearly demonstrated clinically relevant change from baseline across secondary efficacy endpoints, but the patients had more impaired respiratory function at baseline and may as a population have been more sensitive to revelation of benefit over a relatively short time scale. Study 011B was uncontrolled but provides some support for clinical relevance of efficacy benefit. The documented efficacy benefit for LUM/IVA in 12 years and older patients, albeit in a different posology, is also supportive.

3.4. Unfavourable effects

The 24-week, placebo-controlled Study 109 and uncontrolled Study 011B showed that administration of LUM/IVA was overall safe and well tolerated for up to 24 weeks in subjects 6 through 11 years of age. The common AEs observed were mostly manifestations of CF disease. No new safety concerns were identified compared with subjects aged 12 years and older. The Cumulative Study Period, which included the Study 011B and Study110 periods, covered approximately 60 weeks of LUM/IVA exposure in 49 subjects 6 – 11 years old. 18.4% of patients in the LUM/IVA group in study 109 had respiratory adverse events compared with 12.9% in the placebo group; however these percentages are lower than in older patients in studies 103 and 104 where 26.3% of patients on active treatment had respiratory adverse events.

Serial spirometry data demonstrated a transient decline (at 4 – 6 hours post-dose) in ppFEV1 that was generally asymptomatic. The mean decline of -7.7 in LUM/IVA patients could be considered potentially clinically significant; the mean decline was -1.4 in placebo patients. The SmPC include adequate information on these events to inform the treating physicians.

Patients with CF are prone to biliary cirrhosis due to thickened biliary secretions and therefore hepatic transaminase elevation is a common occurrence in the disease. Elevated transaminases have been reported in patients with CF receiving lumacaftor/ivacaftor. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin. In the uncontrolled Study 011B and in Study 109, ALT and AST elevations appeared to be higher than that observed in subjects 12 years of age and older (Studies 103 and 104). These observations are consistent with information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults, and are also consistent with a background rate of 15.3% (ALT/AST >3 × ULN) in placebo-treated subjects of the same age group from a previously completed 24-week IVA monotherapy study (Study VX08-770-103 Part B).

In study 109 there were ~5% more patients with modestly elevated (>3 x ULN) transaminases in the LUM/IVA group. No difference was observed for ALT/AST >5 and 8 × ULN, as well as discontinuations, between the LUM/IVA and placebo groups, and the only SAEs occurred in 2 subjects in the placebo group. In the Cumulative Study Period, which included the Study 011B and Study110 periods, covered approximately 60 weeks of LUM/IVA exposure in 49 subjects. As would be expected, cumulative incidence rates (15.5% overall), of transaminase elevation were higher than in the shorter duration studies. No events of transaminase elevation were severe. The cumulative study period was an uncontrolled, open label study period in which the contribution from longer disease duration versus longer drug exposure cannot be distinguished.

There were no cases of possible drug-related liver toxicity sufficient to satisfy Hy's law. An association between Orkambi and drug induced liver injury cannot be excluded. Because of this, section 4.4 in SmPC includes recommendations for liver function test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of abnormal liver function. The current recommendations for the 12 years and older population are considered sufficient for the 6-11 year old patients.

Blood Pressure data across Studies 109, 011B, and 110 showed that BP levels were variable but generally consistent with previous observations from the LUM/IVA-treated subjects 12 years of age and older (Studies 103 and 104).

The RMP specifies appropriate safety concerns.

3.5. Uncertainties and limitations about unfavourable effects

Transient decline in ppFEV1has been observed in older patients and there was some uncertainty whether the risk may be greater in younger patients with smaller diameter airways. Serial spirometry assessments to evaluate pre- and post-dose ppFEV1 were obtained for a subset of subjects in the 6 – 11 year age group at Day 1, Day 15, Week 16, and Week 24 of Study 109. Although the mean decline in ppFEV1 at 4-6 hours post-dose on Day 1 in study 109 appeared to be steep (-7.7 percentage points) compared to placebo (-1.4%) , there was also very wide variability with wide confidence intervals (95% CI -24.8, 12.8 in LUM/IVA versus -33.9, 17.5 in placebo). Therefore, some placebo treated patients apparently declined more than LUM/IVA patients and the variability may in part reflect the greater unreliability of spirometry measurements that require voluntary effort in young children. Respiratory AESI on Day 1 were 2.9% in LUM/IVA and 4.0% in the placebo group consistent with the asymptomatic nature of the decline. Therefore, the decline in FEV1 does not appear to be associated with respiratory adverse events at the time. The post-dose decline was markedly attenuated by Day 15 and resolved by Week 16. There was also an overall low rate of treatment discontinuation in studies 011 and 109 that was similar in LUM/IVA and placebo groups.

Literature data provide external evidence of a transient, post-dose decline in FEV1, the mechanism being unknown. Data support that the effect is similar in the 6 -11 years age group compared to older patients. More than 80% of patients in the Orkambi studies were already using bronchodilators at study entry which is reflective of use in the CF population at large. Subgroup analysis (subjects with or without bronchodilator use) did not demonstrate any trend suggesting a lower rate of respiratory events in subjects with bronchodilator use. Published studies have examined bronchodilator use as risk minimisation upon initiation of LUM/IVA, with mixed success. Overall therefore there does appear to be insufficient evidence to support additional bronchodilator use or other risk minimisation strategy to cover the initiation of treatment with Orkambi. Furthermore, most patients will have been prescribed bronchodilators. The CHMP expressed concerns in regard to the early decline in ppFEV1, particularly in relation to adequacy of the explanations given for missing spirometric data and whether missing data has led to distortion of ppFEV1 values at later times. As explained by the MAH, a major reason for the large amount of missing spirometric data appears to have been due to the instigation of a different protocol to comply with a modified PIP, mid-way through the study. In Protocol v1.0: There were 117 subjects who received study drug and per protocol were to have serial postdose spirometry measurements conducted at Day 1 and Day 15. Spirometry was performed pre-bronchodilator and predose, and 2 and 4 hours postdose. Protocol v2.0: There were 87 subjects who received study drug and per protocol were to have serial postdose spirometry measurements conducted at Day 1, Day 15, Week 16, and Week 24. On Day 1, spirometry was performed pre-bronchodilator and predose, and at 0.25 to 1 hour, 4 to 6 hours, and 24 hours postdose. On Day 15, Week 16, and Week 24, spirometry was performed pre-bronchodilator and predose, and at 0.25 to 1 hour and 4 to 6 hours postdose.

There were consequently more subjects with postdose spirometry measurements at Day 1 and Day 15 compared to Week 16 and Week 24 because per protocol there were 117 fewer subjects required to have the postdose spirometry assessments at Week 16 and Week 24.

Of subjects who had a ppFEV1 decline $\geq$ 5 percentage points at 4 to 6 hours postdose on Day 1, 53 did not have postdose spirometry at Week 24. Thirty-nine (74%) of these subjects were initially screened under Protocol v1.0 and thus were not required to have postdose spirometry at Week 24 per protocol. The missing spirometry assessments for the remaining 14 subjects are due to a combination of treatment

discontinuation, treatment interruption, pharmacy issue, and dosing error (dosed with Study 110 study drug at Week 24).

Another reason for missed spirometric measurements was due to a change in the scheduling of treatment in relation to the week 24 visit as a result of the protocol amendment. The Day 1 Visit of Study 110 was on the same day as the Week 24 Visit (last Treatment Period visit) of Study 109. Per protocol, subjects who initially screened under Protocol v1.0 were to have the last Study 109 dose the evening before the Week 24 Visit, whereas subjects who initially screened under Protocol v2.0 were to have the last Study 109 dose at the Week 24 Visit (this was done to account for the added postdose spirometry assessments at the Week 24 Visit in Protocol v2.0). Sites were provided with additional training due to the identification of a trend where subjects who initially screened under Protocol v2.0 were inadvertently dosed with Study 110 study drug at Week 24. To minimize any misinterpretation of postdose spirometry data at the Week 24 Visit (placebo and LUM/IVA treatment), postdose spirometry measurements for these subjects were considered invalid and were not included in the spirometry analysis for Study 109. The dosing errors appear can therefore be understood as arising largely from the protocol change rather than from fundamental flaws in study integrity.

Analyses examining the postdose ppFEV1 results for subjects who completed all serial spirometry assessments and for subjects who did not complete all serial spirometry assessments support the conclusion that the missing spirometry data do not impact the interpretation of the serial lung function measurements.

Although the phenomenon of decline in ppFEV1was associated at the time with no respiratory adverse events in this population of patients with stable CF at baseline, the possible implications for patients with co-existent airways hypersensitivity, or for those with unstable CF at the time of treatment initiation, were considered, in case patients predisposed to airways narrowing may require bronchodilator therapy to cover the early period after treatment initiation.

3.6. Effects Table

Effects Table for Orkambi line extension in 6 – 11 year old CF patients homozygous for F508del-CFTR

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Reduction (improvement) from baseline in $LCI_{2.5}$	Treatment difference versus placebo; $p < 0.0001$	LCI unit	LUM 200 / IVA 250 mg q12h	Matched placebo	$LCI_{2.5}$ endorsed for this age group in report from workshop on CF endpoints	EMA/769571/2012
Mean reduction in sweat chloride	Treatment difference versus placebo $p < 0.0001$	mmol/L	LUM 200 / IVA 250 mg q12h	Matched placebo	Pharmacodynamic marker but recommended by CHMP.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Numerical improvement from baseline in BMI and CFR-Q	Change from baseline. No demonstrable benefit over placebo		LUM 200 / IVA 250 mg q12h	Matched placebo	These endpoints are likely to be relatively insensitive to revelation of treatment benefit in patients at a relatively early stage of disease	
Unfavourable Effects						
Decline in ppFEV1	Transient decline in early post-dose period with LUM/IVA	Absolute Percentage point	LUM 200 / IVA 250 mg q12h	Matched placebo	Wide variability. Spirometry unreliable in young children. Further information requested.	
Transaminase elevation	5% more patients in LUM/IVA arm have >3xULN but no difference versus placebo in more severe elevations	%	LUM 200 / IVA 250 mg q12h	Matched placebo	Recognised in older patients as well. No evidence of greater risk in young children. Adequate risk minimisation in place.	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

It is considered that clinical efficacy has been sufficiently demonstrated in CF patients homozygous for F509del-CFTR aged 6 – 11 years administered with the new FDC combination of Orkambi at the proposed posology. Administration of LUM/IVA was overall safe and well tolerated for up to 24 weeks in subjects 6 through 11 years of age. The common AEs observed were mostly manifestations of CF disease. No new safety concerns were identified compared with subjects aged 12 years and older.

Although there are still limited patient numbers in the 6 -11 yrs age range treated for 12 months or more, in the context of this as a rare disease with high unmet need, the safety data are considered in principle sufficient to support long term administration of the new FDC in patients 6-11 years of age. Safety information can also be drawn from the extensive post-marketing experience of Orkambi. An imposed PASS to evaluate use, safety and long term effects of lumacaftor/ ivacaftor therapy in patients aged 6 to 11 years (as part of Study 108) is a condition of the marketing authorisation. There is a clear unmet need in this patient population and the benefits are considered to outweigh the risks.

3.7.2. Balance of benefits and risks

Patients homozygous for F508del-CFTR have a severe form of cystic fibrosis. Orkambi provides a

combination of lumacaftor to correct processing and trafficking of the CFTR conductance channel, with the potentiator action of ivacaftor to enhance channel open probability. Orkambi is currently authorised in the EU for the 12 years and older population. The biochemical defect in the CFTR conductance channel is present from birth and although the disease can take many years to become manifested in full, there is evidence of respiratory and other organ involvement in patients 6 – 11 years even if there is no overt pulmonary dysfunction as measured by spirometry. The aim of the Orkambi line extension was to provide a suitable age-appropriate formulation to treat a younger group of patients (6-11 years), the goal being to modify the disease course by correction or at least improvement in the biochemical defect at a stage of disease where slowing of disease, or possibly pre-emption of respiratory and other consequences of the disease, may be possible.

The line extension is for a new combination of Orkambi with an altered ratio of LUM/IVA that was confirmed by PK modelling for LUM and IVA exposure in the 6 – 11 year old population and is supported by new PK data and a Population PK analysis supplied with the dossier. The data overall support an age cut-off of 11 years with patients moving on to the already authorised combination from the age of 12. The evidence presented is considered to provide sufficient evidence of clinically relevant efficacy benefit in a marker of ventilation inhomogeneity that is consistent with improvement in small airways disease. This is supported by improvement in sweat chloride, consistent with at least partial correction of the defect in the chloride channel protein and a trend to improvement in other efficacy endpoints at a stage of disease where decline in respiratory function is likely to be slow.

An early post-dose, transient, decline in ppFEV1 occurs after initiation of LUM/IVA which is unexplained but does not appear to impede the overall benefit on ventilation homogeneity and spirometry over the longer term. A warning in section 4.4 has been implemented, to avoid misinterpretation of this as lack of efficacy, risking discontinuation.

As observed in studies in older patients, there are modest elevations in transaminases but no evidence that the younger patients are at higher risk. The risk minimisation for the 12 years and older population is considered to be adequate for the younger patients. More generally, the risk minimisation in place for the 12 years and older patients is considered in principle to be adequate for the 6 – 11 year old population, unless additional measures may be required in the early period after treatment initiation to mitigate the risk of decline in ppFEV1 in susceptible patients.

3.8. Conclusions

The overall B/R of Orkambi (age-appropriate formulation) in CF patients 6 – 11 years homozygous for F508del-CFTR is positive and the line extension is approvable.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Orkambi is not similar to Bronchitol, Cayston, TOBI Podhaler 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 and safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of, Orkambi film-coated tablets (100 mg Lumacaftor / 125 mg Ivacaftor) is favourable in the following indication:

Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene (see sections 4.2, 4.4 and 5.1).

The CHMP therefore recommends the extension of the marketing authorisation for Orkambi 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.

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.

Obligation to conduct post-authorisation measures:

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

Description	Due Date
The applicant should conduct a 5-year long-term observational study with lumacaftor/ivacaftor in patients with cystic fibrosis, including also microbiological and clinical endpoints (e.g. exacerbations) according to an approved protocol. The Applicant should submit yearly analyses from December 2017 to 2020 and the final CSR by December 2021.	Final CSR December 2021

Additional Data exclusivity / Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Vertex Pharmaceuticals (Europe) Ltd., taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0220/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Appendices

1. CHMP AR on similarity dated 9 November 2017.
2. CHMP AR on significant clinical benefit in comparison with existing therapies.